Common Drug Review

Pharmacoeconomic Review Report

September 2017

Drug	Ixekizumab (Taltz)
Indication	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Reimbursement request	As per indication
Dosage form	80 mg subcutaneous injection
NOC date	May 25, 2016
Manufacturer	Eli Lilly Canada Inc.

Ixekizumab (Taltz) Common Drug Review Pharmacoeconomic Report was prepared using DeltaPA data from IMS Health Canada Inc. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in dermatology who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

CDR	Common Drug Review
CUA	cost-utility analysis
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol Five-Dimension Health-Related Quality of Life Questionnaire
ICUR	incremental cost-utility ratio
IDC	indirect comparison
IL	interleukin
PASI	Psoriasis Area and Severity Index
QALY	quality-adjusted life-year
SEB	subsequent entry biologic
SF-36	Short-Form (36) Health Survey
SoC	standard of care

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Ixekizumab (Taltz)
Study Question	To quantify the expected costs and benefits of ixekizumab in clinical practice and to compare these expected costs and benefits to those of relevant alternative treatment options in patients with moderate to severe plaque psoriasis who are eligible for systemic treatment
Type of Economic Evaluation	Cost-utility analysis (CUA)
Target Population	Adult patients with moderate to severe plaque psoriasis who are eligible for systemic treatment. Modelled population reflects a mix of biologic-naive and biologic-experienced patients.
Treatment	Ixekizumab 160 mg injection as a starting dose, followed by 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks
Outcome	Quality-adjusted life-years (QALYs)
Comparators	• SoC, defined as combination therapy with methotrexate and phototherapy) • Adalimumab SC 80 mg initially, then 40 mg every other week • Etanercept SC 50 mg twice weekly for three months, then 50 mg weekly • Infliximab (branded product) IV 5 mg/kg at weeks 0,2,6, and then every 8 weeks • SEB infliximab IV (same dosing regimen as branded product) • Ustekinumab SC 90 mg • Secukinumab SC 300 mg at weeks 0, 1, 2, and 3, then monthly • Apremilast 30 mg twice daily, following titration schedule for one week with an average of 30 mg on average
Perspective	Canadian publicly funded health care payer
Time Horizon	Lifetime (45 years)
Results for Base Case	• Compared to SoC, ixekizumab had an incremental cost-utility ratio (ICUR) of $113,023 per QALY. • Based on sequential analysis, SEB infliximab is associated with the lowest ICUR ($85,983 per QALY versus SoC), followed by ixekizumab ($346,946 per QALY versus SEB infliximab).
Key Limitations	• The assumption that patients experience immediate quality of life improvements upon treatment initiation does not reflect available evidence or clinical experience with biologics and serves to overestimate QALY gains for all biologics in relation to SoC. • The use of PASI-to-utility mapping algorithm, rather than directly measured SF-36 scores available from the clinical trials of ixekizumab, introduces uncertainty into the estimated QALYs. • The model time horizon may be inappropriately long given uncertainties regarding long-term effectiveness of biologic therapy. • Patients were assumed to move directly to SoC after failure of initial biologic therapy, which is unlikely to reflect real-world practice where other biologics are likely to be tried. The model permitted treatment sequencing; however, there is insufficient evidence to guide optimal treatment sequence. • Lack of subgroup analysis specifically for biologic-experienced patients. • Assumption in the model that all biologics are associated with a 20% annual discontinuation rate may not be reflective of real-world

	experience, although this is likely a conservative assumption, since older biologic drugs may have higher discontinuation rates than ixekizumab.
CADTH CDR Estimate(s)	• Based on reanalyses to account for some of the above limitations (i.e., assumption of gradual utility gain over drug initiation period, use of a 10-year time horizon, and correction of monitoring and follow-up schedule), CADTH CDR estimated that the ICURs of ixekizumab compared to SoC are $119,564 for the mixed population modelled in the manufacturer's base case, and $128,612 for biologic-experienced patients. The corresponding CADTH CDR base-case ICURs for ixekizumab vs. SEB infliximab were $360,307 and $393,762, respectively. • Price reductions of 16% and 22% are required for the ICUR to fall below $100,000 per QALY versus SoC for the mixed and treatment-experienced populations, respectively. Price reductions of more than 55% are necessary in the CADTH CDR base case for both populations for the ICUR to fall below $50,000 per QALY versus SoC. Price reductions of 22% and 24% are required for the ICUR to fall below $100,000 per QALY versus SEB infliximab for the mixed and biologic-experienced populations respectively, and price reductions of 27% and 28% are necessary for the ICUR to fall below $50,000 per QALY versus SEB infliximab for the same populations. However, price reductions of 23% in the first year of treatment and 14% in subsequent years would be sufficient to achieve cost parity with SEB infliximab.

CDR = Common Drug Review; CUA = cost-utility analysis; ICUR = incremental cost-utility ratio; IV = intravenously; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; SEB = subsequent entry biologic; SC = subcutaneous; SoC = standard of care; vs. = versus.

EXECUTIVE SUMMARY

Background

Ixekizumab (Taltz) is a humanized anti-interleukin (IL)-17A monoclonal antibody indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systematic therapy or phototherapy.[1] The manufacturer is requesting listing of ixekizumab for adult patients in line with the indication.[2] The recommended starting dose of ixekizumab is 160 mg, followed by 80 mg every two weeks for 12 weeks, and then 80 mg every four weeks. Ixekizumab is available as an 80 mg/1 mL pre-filled pen or pre-filled syringe, at a confidential price of $1,519. At the recommended dose, ixekizumab costs $27,342 in the first year of treatment and $19,747 in the each subsequent year.

The manufacturer submitted a cost-utility analysis comparing ixekizumab and other biologic drugs available for the treatment of plaque psoriasis with standard of care (SoC, defined as combination treatment with methotrexate and phototherapy) in adult patients with moderate to severe plaque psoriasis who are candidates for systematic therapy.[3] The analysis was based on a Markov state-transition model using a 45-year time horizon and undertaken from the perspective of the Canadian publicly funded health care system. The manufacturer reported that, compared with treatment with SoC, ixekizumab has an incremental cost-utility ratio (ICUR) of $113,023 per quality-adjusted life-year (QALY). When considering all comparators using a sequential analysis, subsequent entry biologic (SEB) infliximab is associated with the lowest ICUR ($85,983 per QALY versus SoC), followed by ixekizumab ($346,946 per QALY versus SEB infliximab). All other comparator drugs were ruled out, as they were either dominated or extendedly dominated (i.e., they were more costly and less effective than one or more comparators).

Summary of identified limitations and key results

The CADTH Common Drug Review (CDR) identified several limitations of the manufacturer's submission:

- The assumption that patients experience a response measured by the Psoriasis Area and Severity Index (PASI) and improvements to quality of life immediately after treatment initiation does not reflect available evidence or clinical experience with biologic drugs and overestimates QALY gains versus SoC for all biologic comparators.
- The use of a PASI-to-utility mapping algorithm, rather than using directly measured Short-Form (36) Health Survey (SF-36) scores available from the clinical trials of ixekizumab, introduces uncertainty into the estimated QALYs.
- The model time horizon (45 years) may be inappropriate, given uncertainties regarding long-term effectiveness of biologic therapy, although this affects all comparators and is unlikely to bias results in favour of ixekizumab.
- Patients were assumed to move directly to SoC after failure of initial biologic therapy, which is unlikely to reflect real-world practice, in which other biologics are likely to be tried. The model permitted treatment sequencing; however, there is insufficient clinical evidence to guide what the optimal treatment sequence in the model should be.
- Subgroup analysis specifically for biologic-experienced patients was lacking. (The cohort in the model represents a mixed population of biologic-naive and biologic-experienced patients, per the patient population enrolled in the UNCOVER trials.)
- The model contained an assumption that all biologics are associated with a 20% annual discontinuation rate, which may not be reflective of real-world experience. However, this is likely a conservative assumption, since older biologic drugs may have higher discontinuation rates than newer ones such as ixekizumab, according to the clinical expert consulted by CADTH CDR.

- There are limitations of the manufacturer's indirect treatment comparison, from which estimates of PASI response were derived for the model: primarily the lack of data beyond 12 to 16 weeks and the lack of specific subgroup data on biologic-experienced patients.
- Resource use (i.e., monitoring schedule) for patients using biologic therapy was not considered reflective of clinical practice.

When possible, CADTH CDR addressed these limitations through one-way sensitivity analysis and a CADTH CDR base case consisting of a multi-way sensitivity analysis incorporating a linear gain in utility over the treatment-initiation period, a 10-year time horizon, and corrected resource use. Cost-effectiveness was also estimated specifically for biologic-experienced patients. None of these revisions resulted in substantial changes in the estimated cost-effectiveness of ixekizumab compared with the manufacturer's base case.

Conclusions

When accounting for the identified limitations, the CADTH CDR base-case ICUR for ixekizumab versus SoC was $119,564 for the mixed cohort and $128,612 for biologic-experienced patients only. The corresponding CADTH CDR base-case ICURs for ixekizumab versus SEB infliximab were $360,307 and $393,762, respectively. Price reductions of 22% and 24% are required for the ICUR to fall below $100,000 per QALY versus SEB infliximab (the most cost-effective biologic drug in the analysis) for the mixed and biologic-experienced populations, respectively. Price reductions of 27% and 28% are necessary for the ICUR to fall below $50,000 per QALY versus SEB infliximab for the same populations. It should be noted that price reductions of this magnitude would lower the per-patient cost of ixekizumab to below that of SEB infliximab; price reductions of 23% in the first year of treatment and 14% in subsequent years would be sufficient to achieve per-patient cost parity with SEB infliximab. Given the lack of significant differences in efficacy between ixekizumab and secukinumab or SEB infliximab, and the modest QALY differences between these drugs, there appears to be limited justification for a price premium for ixekizumab.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

Summary of the manufacturer's pharmacoeconomic submission

The manufacturer submitted a cost-utility analysis (CUA) comparing ixekizumab and other biologic drugs (adalimumab, etanercept, ustekinumab 45 mg, ustekinumab 90 mg, infliximab [Remicade], subsequent entry biologic [SEB] infliximab, and secukinumab) with standard of care (SoC, defined as combination therapy with methotrexate and phototherapy) among adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.[3] The model population was assumed to have characteristics in alignment with the UNCOVER trials[4]: the mean age was 45 years, 66% were male, and the mean body weight was 91.0 kg. Although the base-case analysis is described in the manufacturer's submission as reflective of biologic-naive patients, the UNCOVER trials included varying proportions of biologic-experienced patients.[4,5] Therefore, the cohort and treatment effects applied in the model actually represent a mixed biologic-naive and biologic-experienced population, although the model included an option to specifically model cost-effectiveness for biologic-experienced patients. The CUA was based on a Markov state-transition model using a 45-year time horizon and a cycle length of one month. All costs and outcomes were discounted at a rate of 5% annually, and the analysis was undertaken from the perspective of the Canadian publicly funded health care system.

The health states in the model consisted of a "trial period," a long-term "maintenance" period, "SoC," and "death" (Figure 1). Among patients receiving ixekizumab or another biologic drug, response to treatment (defined as achievement of PASI 75 in the base case) was assessed at the end of a drug-specific trial period (12 weeks for ixekizumab, secukinumab, infliximab, SEB infliximab, adalimumab, and etanercept, and 16 weeks for ustekinumab 45 mg and 90 mg). Patients who responded to treatment moved to the maintenance state; whereas, non-responders moved to SoC in the base case (although the model allowed for subsequent treatments to be tried before moving to SoC). Patients in the maintenance state remained there until they discontinued therapy and moved to SoC in the base case (or subsequent treatment, if specified) owing to loss of treatment efficacy or onset of adverse events, or until they died. Patients who transitioned to SoC remained in this state for the remainder of the time horizon or until death. Response to treatment in the trial period was based on Psoriasis Area and Severity Index (PASI)-level results from the manufacturer-submitted indirect comparison (IDC).[6] The PASI response in the SoC state was assumed to be constant and was derived from the placebo response rate from the manufacturer-submitted IDC. Patients could enter the death state from any health state based on age-specific mortality rates from Statistics Canada. Mortality associated with psoriasis was not included in the base-case analysis. A dropout rate of 20% was assumed with all treatments for patients in the maintenance state, to account for loss of efficacy or onset of adverse events; this value was based on previously reported literature values.[7-9]

Health state utilities in the model were based on PASI response categories (i.e., PASI < 50, PASI 50 to 74, PASI 75 to 90, PASI 90, and PASI 100). Each successive PASI-response category was associated with a utility increment based on a study by Pan et al.[10] that mapped PASI response to Dermatology Life Quality Index (DLQI), which was subsequently mapped to EuroQol Five-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) utilities. The total utility associated with each treatment was based on the proportion of patients in the different PASI-response categories at each cycle.

The costs considered in the model were those associated with drug acquisition, physician visits, and monitoring tests and adverse events. Resource-use estimates were based on Canadian product monographs, expert opinion, and the published literature. The cost of ixekizumab was based on the

manufacturer's submitted price, and the costs of all other medications were obtained from the Ontario Drug Benefit Formulary[11] and IMS Brogan DeltaPA.[12] The costs of physician visits were obtained from the Ontario Health Insurance Plan schedule of benefits,[13] and the costs of laboratory tests were taken from the CADTH Therapeutic Review report on drugs for pulmonary arterial hypertension.[14]

Manufacturer's base case

The manufacturer reported in its base case that ixekizumab is associated with a total cost of $88,990 and a gain in quality-adjusted life-years (QALYs) of 1.59. When compared with SoC, ixekizumab was $70,626 more costly and associated with a gain of 0.625 QALYs, for an incremental cost-utility ratio (ICUR) of $113,023 per QALY. When considering all comparators using a sequential analysis, SEB infliximab is associated with the lowest ICUR ($85,983 per QALY) versus SoC, followed by ixekizumab ($346,946 per QALY versus SEB infliximab; Table 9). All other comparators were either dominated (i.e., less effective and more costly than one or more alternatives) or extendedly dominated (i.e., less effective than a combination of less costly alternatives). When comparing ixekizumab with the other available anti-interleukin (IL)-17A biologic drug, secukinumab, ixekizumab is $1,983 more costly and is associated with a gain of 0.055 additional QALYs.

Summary of manufacturer's sensitivity analyses

The manufacturer conducted a range of one-way deterministic sensitivity analyses. Results were most sensitive to the discount rate for costs, with ICURs ranging from $109,057 per QALY with a 6% discount rate for costs to $138,542 with no discounting. Results were also sensitive to the discount rate for outcomes, the cost of ixekizumab, annual discontinuation rate, and efficacy estimates.

A probabilistic sensitivity analysis was also reported by the manufacturer; all simulations were in the northeastern quadrant of the cost-effectiveness plane (indicating that ixekizumab costs more and produces more QALYs than SoC). Of note, while the manufacturer's base-case ICUR was $113,026 per QALY, the probabilistic sensitivity analysis revealed that ixekizumab only has a 60% probability of being cost-effective at a willingness-to-pay threshold of $120,000 per QALY, indicating considerable uncertainty in the results. At a willingness-to-pay threshold of $150,000, the probability of that ixekizumab is cost-effective is approximately 90%.

Limitations of manufacturer's submission

- **Assumptions regarding utility gain during the trial period**
  In the base case, patients received the benefits of treatment (in terms of quality-of-life improvements) immediately upon starting treatment. In practice, biologic drugs often require several weeks until PASI 75 response is achieved. This was demonstrated in UNCOVER-3, in which the proportion of patients achieving PASI 75 did not reach a maximum until week 12.[5] The clinical expert further confirmed that PASI 75 response would likely be seen at four to 12 weeks in most patients treated with a biologic drug. As a result, CADTH Common Drug Review's (CDR's) preferred assumption is that there is a gradual linear gain in quality of life throughout the trial period, rather than an immediate gain at the beginning of treatment.
- **Uncertainty regarding validity of mapped utility values**
  The manufacturer used utility values from Pan et al.,[10] in which both PASI and DLQI scores were recorded in two phase 3 clinical trials of ustekinumab. PASI scores were mapped to EQ-5D utilities using linear regression mapping, based on patients in the Health Outcomes Data Repository database for whom both DLQI and EQ-5D values were recorded.[10] The use of this indirect method involving disparate data sources, and uncertainty regarding the correlation between PASI and DLQI

and between DLQI and EQ-5D,[15-17] introduced uncertainty regarding the validity of the estimated QALYs from the manufacturer's model. CADTH CDR identified alternative utility-mapping studies[7,18,19] associating PASI and DLQI based on data from drugs and patient populations that differed from those in Pan et al. However, CADTH CDR considered that the Pan et al. study[10] was the most appropriate choice for mapped values, given the high proportion of Canadian patients in the ustekinumab trials used to derive EQ-5D values. However, CADTH CDR noted that directly measured Short-Form (36) Health Survey (SF-36) scores were available from the UNCOVER trials, and that use of directly measured utilities in cost-effectiveness models is preferred when possible. The manufacturer did not provide justification for use in the model of mapped values from Pan et al.[10] rather than directly measured SF-36 values.

- **Uncertainty regarding appropriateness of model time horizon**
  The manufacturer considered a lifetime time horizon (45 years) in the base case. However, this may be longer than appropriate when evaluating biologic monotherapy followed by SoC, since "biologic fatigue," the loss of efficacy of a biologic medication with long-term use, may occur.[20] Available evidence suggests that treatment failure typically occurs within the first one to two years of treatment. A retrospective cross-sectional study by Levin et al.[21] found that the mean time to discontinuation for all biologic drugs was 242 days; whereas, the longest average time until treatment discontinuation was 292 days (for infliximab). Further, in a retrospective chart review of Canadian patients, the longest median duration of therapy until discontinuation due to adverse events was 27.2 months (with ustekinumab).[22] When CADTH CDR compared modelled drug survival results at two years against this study,[22] the results broadly agreed, indicating that modelled dropout rates are reasonably reflective of real-world discontinuation rates. However, modelling of discontinuation alone cannot fully address the uncertainty regarding long-term effectiveness over a lifetime time horizon. The use of a shorter time horizon can help mitigate the effects of this uncertainty.
- **Assumptions regarding post-discontinuation management do not reflect clinical practice**
  In its base case, the manufacturer assumes that patients receive active therapy followed by lifetime SoC upon treatment discontinuation. In practice, treatment is unlikely to proceed in this manner since other biologic drugs (as well as combinational and rotational therapy) are likely to be tried before resorting to SoC.[23] Although the manufacturer provided the option to assess treatment sequences in the submitted model, there is a paucity of data to guide optimal treatment sequences. Furthermore, psoriasis treatment guidelines do not provide recommendations regarding optimal biologic treatment sequence after failure of an initial biologic drug.[24-26]
- **Resource use**
  The manufacturer assumed that patients receiving a biologic drug would receive one annual follow-up visit with a physician and an annual chest X-ray during the maintenance phase of treatment. CADTH CDR's consulting clinical expert noted that the proposed monitoring schedule may not reflect clinical practice. In particular, patients would likely receive two follow-up visits annually and no chest X-rays, except in the minority of patients who have tuberculosis, risk factors for tuberculosis, or overt respiratory problems. Further, secukinumab was the only biologic drug for which patients received a chest X-ray during the trial period in the manufacturer's base case. This was not justified, and there was no indication in the secukinumab product monograph that patients should receive a chest X-ray.[27] This assumption slightly biases results against secukinumab. In its base case, CADTH CDR assumed that patients received two annual follow-up visits and no chest X-rays during the maintenance phase.

- **Lack of subgroup analyses for biologic-experienced patients**
  The manufacturer's base-case results reflected a mixed population of biologic-naive and biologic-experienced patients. Among patients who have experienced a previous treatment failure on a biologic drug, response to subsequent biologic drugs may be attenuated, according to the clinical expert consulted by CADTH CDR. While the manufacturer did not provide subgroup analyses by treatment experience in its IDC,[6] subgroup analyses in the clinical study reports for UNCOVER 1, 2, and 3[4,5] found that PASI response is attenuated among some subgroups of treatment-experienced patients. In the absence of subgroup data in the IDC, CADTH CDR used the manufacturer-provided values from a Danish cohort study that estimated the decrease in treatment efficacy of a second biologic drug after failure of a previous biologic drug.[9] This study suggested that, among patients starting a new biologic drug, those who were biologic-naive had higher odds (odds ratio 1.24) of treatment continuation compared with biologic-experienced patients. This value was used by CADTH CDR to estimate the cost-effectiveness of ixekizumab specifically among patients who had previously experienced treatment failure on a biologic drug.
- **Limitations of manufacturer's indirect treatment comparison**
  As noted in the CADTH CDR clinical review, limitations of the manufacturer-submitted IDC include unknown reliability of screening software and its potential impact on study conclusions, and lack of information about patients' previous treatments and outcomes, which may have introduced heterogeneity in baseline patient characteristics across included trials. Given the chronic nature of plaque psoriasis, the lack of trial data beyond 12 to 16 weeks, was also a limitation of the IDC.
- **Assumptions regarding equal treatment discontinuation rates**
  The manufacturer assumed that all treatments were subject to a 20% annual all-cause withdrawal rate reflecting loss of efficacy and/or onset of adverse events. This figure aligned with the assumptions used in the York model[7] and previous literature sources.[8,9] However, in practice, rates of withdrawal have been observed to differ across biologic drugs and to be higher with less effective biologic drugs and those associated with higher rates of adverse events.[21] In addition, different biologic drugs exhibit different response-maintenance profiles after the trial period,[28] further calling into question the assumption of equal withdrawal rates. In practical terms, however, this assumption is likely conservative with respect to ixekizumab, in light of feedback from the CADTH CDR clinical expert indicating that some of the older anti–tumour necrosis factor drugs may exhibit annual withdrawal rates in clinical practice as high as 30% to 40%.

CADTH Common Drug Review Reanalyses

To account for the limitations identified above, the following analyses were undertaken (Table 2).

1. Linear utility gain during trial period

Based on the results of the UNCOVER trials[5] and input from the clinical expert, patients were assumed to gain utility in a linear fashion over the trial period, rather than accruing all benefits at treatment initiation. This resulted in a slight increase in the ICUR for ixekizumab versus SoC to $118,260 per QALY, and for ixekizumab versus SEB infliximab to $355,412 per QALY.

2. Use of a 10-year time horizon

CADTH CDR used a model time horizon of 10 years to avoid the considerable uncertainty in long-term costs and consequences over the 45-year duration of the manufacturer's base-case analysis. This resulted in a slight increase in the ICUR for ixekizumab versus SoC to $113,801 per QALY, and for ixekizumab versus SEB infliximab to $351,035 per QALY.

3. Corrected resource utilization for patients using a biologic

Patients receiving a biologic drug were assumed to receive two follow-up physician visits annually. Further, patients taking biologic drugs did not incur the costs of chest X-rays during the maintenance period, given that only a small minority of patients are expected to require a chest X-ray. Finally, patients on secukinumab were assumed to not receive a chest X-ray. The resulting change in the ICURs compared with the manufacturer's base case was negligible.

4. Results for biologic-experienced patients

To estimate cost-effectiveness in biologic-experienced patients, the manufacturer-submitted model allowed incorporation of the odds ratio of 1.24 reported in a Danish study of treatment continuation among biologic-naive versus biologic-experienced patients. Treatment continuation rates and PASI response rates were decreased accordingly. The resulting ICURs for ixekizumab in biologic-experienced patients were $119,564 per QALY versus SoC and $360,307 per QALY versus SEB infliximab. Since the base-case cohort in the manufacturer's model represents a mixed population of biologic-naive and biologic-experienced patients, CADTH CDR noted that application of the 1.24 factor may over-penalize PASI response rates in the model.

5. Alternative PASI-to-utility mapping algorithms

Considering the utilities from alternative mapping studies[7,18,19] in the context of the manufacturer's base-case analysis resulted in ICURs for ixekizumab of $148,238 to $178,967 per QALY compared with SoC. Applying these alternative utilities to CADTH CDR's base-case estimates resulted in ICURs of $157,034 to $194,509 per QALY for the manufacturer's base-case cohort consisting of biologic-naive and biologic-experienced patients, and $168,995 to $211,783 per QALY for biologic-experienced patients only (Table 14). In both instances, results of the sequential analysis did not change substantially.

The CADTH CDR base-case analysis consisted of a multi-way sensitivity analysis incorporating the linear gain in utility over the trial period, 10-year time horizon, and corrected costs of SoC; detailed results are given in Table 10 and Table 11. The utility values from Pan et al.[10] were retained in the CADTH CDR base case owing to the high proportion of Canadian patients in the ustekinumab trials used to derive PASI and DLQI values in this study.

TABLE 2: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSES

Scenario		ICUR ($ per QALY) for ixekizumab vs. SoC	Sequential ICUR of ixekizumab
	Manufacturer's base case	*$113,023*	*$346,946 vs. SEB infliximab*
1	Linear utility gain during trial period	$118,260	$355,412 vs. SEB infliximab
2	10-year time horizon	$113,801	$351,035 vs. SEB infliximab
3	Corrected resource utilization	$113,026	$346,000 vs. SEB infliximab
4	Biologic-experienced patients	$120,496	$378,564 vs. SEB infliximab
1-3	**CADTH CDR base case**	**$119,564**	**$360,307 vs. SEB infliximab**
1-4	**CADTH CDR base case – biologic-experienced patients**	**$128,612**	**$393,762 vs. SEB infliximab**

CDR = Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SEB = subsequent-entry biologic; SoC = standard of care; vs. = versus.

CADTH CDR Price-Reduction Analysis

When considering the manufacturer's base case, a reduction of 11% would be necessary for the ICUR of ixekizumab versus SoC to fall below $100,000, and a reduction of more than 50% would be necessary for the ICUR of ixekizumab to fall below $50,000 per QALY versus SoC. In CADTH CDR's base case, a price reduction of 16% would be necessary for the ICUR to fall below $100,000 per QALY for biologic-experienced patients, and 22% for the ICUR to fall below $100,00 per QALY for the manufacturer's base-case cohort consisting of both biologic-experienced and biologic-naive patients. A price reduction of more than 55% would be necessary to achieve ICURs of below $50,000 per QALY versus SoC for both populations (Table 12).

CADTH CDR also considered the impact of price reductions compared with SEB infliximab, which was the only other biologic drug on the cost-effectiveness frontier. In the manufacturer's base case, price reductions of 22% and 26% would be necessary for the ICUR of ixekizumab to fall below $100,000 per QALY and $50,000 per QALY, respectively. In CADTH CDR's base case for the mixed biologic-naive and biologic-experienced population, the necessary price reductions would be 22% and 27% for the two thresholds, respectively. In CADTH CDR's base case for a biologic-experienced population, the necessary price reductions would be 24% and 28%, respectively. It should be noted that price reductions of 24% or higher would result in lower annual per-patient treatment costs for ixekizumab than for SEB infliximab (although total treatment costs would still be higher with ixekizumab because of its greater efficacy and higher continuation rates compared with SEB infliximab). A price reduction of 23% would result in per-patient cost parity with SEB infliximab in the first year of treatment and a 14% reduction would result in cost parity in subsequent years. Details are given in Table 13.

Issues for consideration

- CADTH CDR is currently reviewing SEB etanercept for use in rheumatoid arthritis and ankylosing spondylitis.[29] Given that etanercept is approved for the treatment of plaque psoriasis, it is anticipated that SEB etanercept may become available for the same indication. A price reduction of 17% or more from the price of reference etanercept (Enbrel) would be sufficient to make it the least costly biologic for plaque psoriasis, as its annual cost during maintenance therapy would be less than $17,063 (the cost of SEB infliximab, which is currently the least costly biologic). This would set a new lower bound for the least costly biologic reimbursed for the treatment of moderate to severe plaque psoriasis.
- Given its common pharmacological mechanism (anti-IL-17A), secukinumab is the closest comparator to ixekizumab. Per the manufacturer's base case, ixekizumab is associated with an incremental gain of 0.055 QALYs compared with secukinumab over a 45-year model horizon, corresponding to less than 21 quality-adjusted days. In CADTH CDR's base case, the incremental difference is 18 quality-adjusted days for the base-case cohort consisting of both biologic-naive and biologic-experienced patients, and 13 days for biologic-experienced patients only. Given the relatively small magnitude of these differences, and since ixekizumab was not statistically superior to secukinumab on most efficacy measures in the manufacturer's IDC, comparison of drug costs alone (i.e., a cost-minimization approach) for ixekizumab versus secukinumab may be an appropriate basis for comparing these products. A similar argument could be applied in comparing ixekizumab with SEB infliximab (the most cost-effective comparator and the only one, apart from ixekizumab, that was not dominated in the analysis), since there were no significant differences in efficacy between the two drugs in the IDC and QALY differences were modest (0.065 QALYs or 24 quality-adjusted days).

Patient input

Feedback was received by CADTH CDR from the Canadian Skin Patient Alliance. Patients noted that the symptoms of plaque psoriasis have a significant detrimental impact on quality of life, psychosocial functioning, ability to undertake the activities of daily living, and maintenance of gainful employment. This was accounted for in the model by including utility gains associated with improvements in disease status, as measured by PASI response. Patients also noted that there is a substantial burden on caregivers, including an increased need for cleaning owing to skin flaking, time needed to take patients to phototherapy and infusion clinics, and overall negative emotional burden. Caregiver burden was not accounted for in the model, as the analysis was performed from the perspective of the health care system.

Concerns regarding treatments for plaque psoriasis included cost, side effects, and time commitments for infusion or phototherapy. Patients also noted that "biologic fatigue," the loss of efficacy of a biologic medication with long-term use, is a concern. Patients who had experience with ixekizumab noted that it was effective in terms of the extent and severity of lesions, as reflected by the manufacturer's inclusion of PASI response in the model.

Conclusions

When accounting for the identified limitations, the CADTH CDR base-case ICUR for ixekizumab versus SoC was $119,564 for the mixed cohort and $128,612 for biologic-experienced patients only. The corresponding CADTH CDR base-case ICURs for ixekizumab versus SEB infliximab were $360,307 and $393,762, respectively. Price reductions of 16% and 22% are required for the ICUR to fall below $100,000 per QALY versus SoC for the mixed and treatment-experienced populations, respectively. Price reductions of more than 55% are necessary in the CADTH CDR base case for both populations for the ICUR to fall below $50,000 per QALY versus SoC. Price reductions of 22% and 24% are required for the ICUR to fall below $100,000 per QALY versus SEB infliximab (the most cost-effective biologic in the analysis) for the mixed and biologic-experienced populations respectively, and price reductions of 27% and 28% are necessary for the ICUR to fall below $50,000 per QALY versus SEB infliximab for the same populations. Price reductions of this magnitude would result in lower annual per-patient treatment costs for ixekizumab than for SEB infliximab (although total treatment costs would still be higher with ixekizumab because of its greater efficacy and higher continuation rates compared with SEB infliximab). Price reductions of 23% in the first year of treatment and 14% in subsequent years would be sufficient to achieve per-patient cost parity with SEB infliximab. Given the lack of significant differences in efficacy between ixekizumab and secukinumab or SEB infliximab, and the modest QALY differences between these drugs, there appears to be limited justification for a price premium for ixekizumab.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed appropriate by the clinical expert consulted by CADTH Common Drug Review. Costs are manufacturer's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as a result, the reported costs may not represent the actual costs to public drug plans.

TABLE 3: COST-COMPARISON TABLE FOR PLAQUE PSORIASIS

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Cost ($)
Biologics					
Ixekizumab (Taltz)	**80 mg**	**Pre-filled syringe**	**$1,519.00**[a]	**160 mg initial dose, 80 mg at 2, 4, 6, 8, 10, and 12 weeks; followed by 80 mg every 4 weeks**	**First year:$27,342** **Subsequent years: $19,747**
Adalimumab (Humira)	40 mg/ 0.8 mL	Syringe or pen	$769.9700	80 mg initial dose, 40 mg every other week starting 1 week after initial dose	First year: $21,559 Subsequent years: $20,019
Etanercept (Enbrel)	50 mg/mL 25 mg/vial	Syringe or pen Vial	$395.3900 $197.6350	50 mg twice weekly for 12 weeks, then 25 mg twice weekly	First year: $25,300[b] Subsequent years: $20,554
Infliximab (Remicade)	100 mg/vial	Vial	$962.6800[c]	5 mg/kg/dose, for 3 doses (0, 2, 6 weeks) then 5 mg/kg every 8 weeks	First year: $38,507[d] Subsequent years: $31,287
SEB Infliximab (Inflectra)			$525.0000		First year: $21,000 Subsequent years: $17,063
Secukinumab (Cosentyx)	150 mg/mL	Pre-filled syringe	$1645.0000 per 300 mg dose[e] (2 × 150 mg syringes per package)	300 mg SC injection at weeks 0, 1, 2, and 3, then monthly injections starting at week 4	First year: $26,320 Subsequent years: $19,740
Ustekinumab (Stelara)	45 mg/ 0.5 mL 90 mg/1 mL	Pre-filled syringe	$4,593.1400 (per 0.5 mL and 1 mL vial)	Patients < 100 kg—45 mg at weeks 0 and 4, followed by 45 mg every 12 weeks thereafter (same for > 100 kg, except 90 mg)	First year: $22,966 Subsequent years: $20,669[f]

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Cost ($)
Conventional Systemic Treatments					
Methotrexate	2.5 mg 10 mg 10 mg/mL 25 mg/mL	Tab Tab Vial Vial	$0.6325 $2.7000[g] $12.4800/2 mL injection $8.9200/2 mL injection	10 mg to 25 mg by mouth *or* IM Weekly	$132 to $329 $232 to $325
Cyclosporine (Neoral)	10 mg 25 mg 50 mg 100 mg	Cap	$0.6238 $0.9952 $1.9400 $3.8815	2.5 mg/kg daily (rounded to 200 mg/day) (max 5 mg/kg/day)	$2,833[h]
Acitretin (Soriatane)	10 mg 25 mg	Cap	$2.3573 $4.1400	25 mg to 50 mg daily	$1,507 to $3,014
Phosphodiesterase-4 Inhibitor					
Apremilast (Otezla)	10 mg 20 mg 30 mg	Tab	$19.2822[i]	30 mg twice daily	First year: $14,057[j] Subsequent years: $14,076

Cap = capsule; IM = intramuscularly; SC = subcutaneously; Tab = tablet.
[a] Manufacturer's submitted price.
[b] First-year cost includes use of 50 mg syringe for the first 12 weeks followed by use of 25 mg vials. In subsequent years, patients are assumed to use 25 mg vials exclusively. Costs are $20,560 if 50 mg syringes are used.
[c] Source: Alberta formulary (April 2016).[30]
[d] Assumes wastage of partially used vials. Eight treatments first year, 6.5 average subsequent years. Note: Average weight was assumed to be 91 kg, per manufacturer's trials and values used in models.
[e] Delta PA, manufacturer's list price, accessed June 2016.[12]
[f] Five treatments first year, 4.5 average subsequent. Price for 45 mg and 90 mg is the same.
[g] Source: Saskatchewan formulary (April 2016).[31]
[h] Lower value assumes 200 mg/day, upper end assumes dosage for average body weight from UNCOVER trials.[4,5]
[i] Delta PA, manufacturer's list price, accessed June 2016.[12]
[j] First year includes titration period with equivalently priced 10 mg and 20 mg pills.
Source: Ontario Drug Benefit (April 2016),[11] except where noted.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS IXEKIZUMAB RELATIVE TO STANDARD OF CARE?

Ixekizumab Versus SoC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$113,023 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year; SoC = standard of care.

Ixekizumab Versus Adalimumab	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$117,904 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year.

Ixekizumab Versus Etanercept 50 mg	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$93,852 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year.

Ixekizumab Versus Ustekinumab 45 mg	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$111,745 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year.

Ixekizumab Versus Ustekinumab 90 mg	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$117,364 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year.

Ixekizumab Versus Secukinumab	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)			X			
Drug treatment costs alone			X			
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	$36,176 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year.

Ixekizumab Versus Infliximab	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)	X					
Drug treatment costs alone	X					
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Ixekizumab dominates infliximab					

CE = cost-effectiveness; N/A = not applicable.

Ixekizumab Versus Subsequent Entry Biologic Infliximab	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$346,946 per QALY					

CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	YES/ GOOD	SOMEWHAT/ AVERAGE	NO/POOR
Are the methods and analysis clear and transparent?		X	
Comments	Model fails to respond to changes in certain inputs, e.g., number of phototherapy sessions assumed in SoC. However, this likely has minimal impact on the results. Providing discounted QALYs and costs in the Markov traces would have been of interest, as would the option to produce cost-effectiveness planes comparing all treatments simultaneously.		
Was the material included (content) sufficient?	X		
Comments			
Was the submission well organized and was information easy to locate?	X		
Comments			

QALY = quality-adjusted life-year; SoC = standard of care.

TABLE 6: AUTHORS INFORMATION

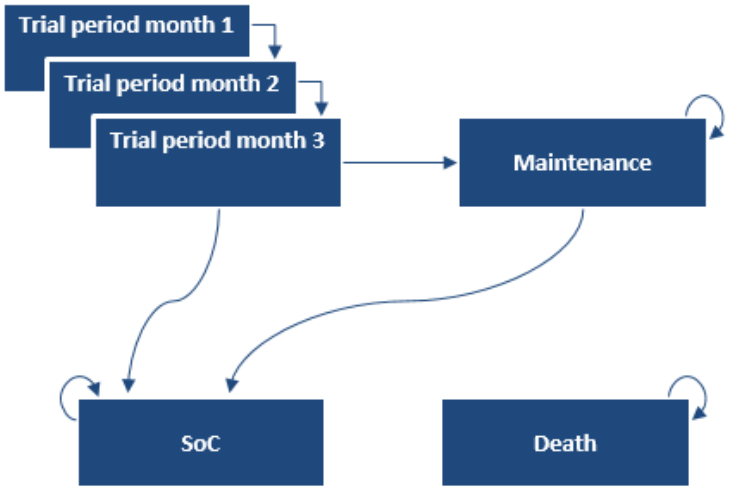
Authors of the pharmacoeconomic evaluation submitted to CADTH CDR
☐ Adaptation of global model/Canadian model done by the manufacturer
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's model structure

FIGURE 1: IXEKIZUMAB MODEL STRUCTURE



Source: Manufacturer's pharmacoeconomic submission.[3]

TABLE 7: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Efficacy inputs to the economic model were from a manufacturer-commissioned IDC.[6] Efficacy of ixekizumab itself was established in 3 pivotal phase 3 trials (UNCOVER-1, -2, and -3)[4,5] Lower efficacy of biologic treatment after failure of a previous biologic was based on the results of a Danish prospective cohort study by Gniadecki et al.[9] The results of the study were that biologic-naive patients had an higher odds of treatment continuation (odds ratio 1.24) compared to biologic-experienced patients. This was applied in the model to both the treatment discontinuation rate and the PASI response rates.	As noted in the CADTH CDR clinical report, the IDC was found to be of sufficient quality. In the absence of alternative data sources the use of the Gniadecki et al. study was found to be appropriate.
Baseline cohort characteristics	Baseline patient age is 45 years, 66% males, and an average weight of 91.0 kg based on values from the UNCOVER trials (UNCOVER-2 and UNCOVER-3).[4] Since the UNCOVER trials included both biologic-naive and biologic-experienced populations, the model cohort also reflects a mixed population.	Baseline patient characteristics were deemed reflective of Canadian practice by clinical expert.
Utilities	The utility gain associated with PASI response was based on a mapping study by Pan et al.,[10] in which PASI values were mapped to DLQI values, which in turn were mapped to EQ-5D scores.	Uncertainty is inherent in any mapping exercise, and this was assessed by CADTH CDR through use of alternative mapping algorithms.

Data Input	Description of Data Source	Comment
		Of note, SF-36 was measured as an outcome in the UNCOVER trials, thus directly elicited utilities could have been used.
Resource use	Treatment and monitoring costs were based on Canadian product monographs and expert opinion.	Sources were considered appropriate. Questionable assumptions regarding monitoring and follow-up were assessed by CADTH CDR in its base case, but these had minimal impact on the results.
Discontinuation rates	The dropout rate was assumed to be 20% per year to reflect loss of efficacy or onset of adverse events. These values were based on the assumptions used in the York model[7] and results from the literature.[8,9]	While the use of a 20% annual rate for all treatments has precedents in other evaluations and has support from literature sources, differential discontinuation has been noted in other studies[21,28] and by CADTH CDR's clinical expert. This is thought to be a conservative assumption on the manufacturer's part, as the discontinuation rate with ixekizumab may be lower than with anti-TNF biologic drugs.
Adverse events (Indicate which specific adverse events were considered in the model)	Costs of serious AEs (non-melanoma skin cancer, malignancy other than non-melanoma skin cancer, and severe infections) could be included as an option in the manufacturer's model but were not included in the base case. Incidence rates of AEs for ixekizumab were based on phase 3 ixekizumab trials;[4,5] whereas, rates for other biologic drugs were obtained from Summaries of Product Characteristics and literature sources.[32-34] Costs of treatment for AEs were based on a report on the cost of hospital stays from the Canadian Institute for Health Information[35] and a report on the economic burden of skin cancer.[36]	Appropriate, reflects approach used in secukinumab submission to NICE. Applying costs of serious AEs to both manufacturer and CADTH CDR's base case did not impact results substantially.
Mortality	Background mortality was based on age- and gender-specific rates from Statistics Canada data. The model includes an option to include an increased risk of mortality (hazard ratio of 1.5) for patients with severe psoriasis, based on a UK-based population cohort study.[37]	Appropriate. The impact of psoriasis on mortality remains a contentious issue. Excluding psoriasis-related mortality from the base case is appropriate. It is also likely a conservative assumption, as it would bias results against more efficacious drugs. Including an increased mortality risk had a minimal effect on ICURs (ICUR in the manufacturer's base case increased from $113,026 to $113,076 per QALY.)

Data Input	Description of Data Source	Comment
Costs		
Drug	• Ixekizumab – manufacturer's submitted confidential price • Comparators – from the Ontario Drug Benefit Formulary (2016)[11] and from IMS Brogan DeltaPA[12]	Appropriate
Administration	• Costs of injections were not considered separately; instead, they were included in administration costs of drugs themselves. • Components of SoC, schedule of follow-ups, and laboratory tests were based on expert opinion. Costs of physician visits and laboratory tests were based on the Ontario Schedule of Benefits [11] and values cited in a previous CADTH report on pulmonary arterial hypertension.[14]	The CADTH CDR clinical expert noted that frequency of follow-up for biologic drugs is likely more frequent (twice yearly physician visits versus once yearly). Patients are also unlikely to receive chest X-rays unless they have a positive tuberculosis test or obvious respiratory concerns. Further, the inclusion of an initial chest X-ray only for secukinumab was not justified. This assumption serves to bias results against secukinumab. These were assessed in CADTH CDR's base case.

AE = adverse event; CDR = Common Drug Review; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol Five-Dimension Health-Related Quality of Life Questionnaire; ICUR = incremental cost-utility ratio; IDC = indirect comparison; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; SF=36 = Short-Form (36) Health Survey.

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Cohort composition reflected clinical practice	Appropriate per clinical expert
PASI response is constant across the model horizon	Possibly inappropriate, as biologic fatigue is a noted phenomenon[20] and patients are likely to experience a gradual decrease in PASI response rather than immediate loss of efficacy implied by the annual 20% withdrawal rate for all comparators. CADTH CDR acknowledges a paucity of data on the natural history of PASI response. It is unknown how this could affect cost-effectiveness estimates.
Adverse events are not considered in the base case	Appropriate, given the lack of data to indicate substantial differences between the treatments
Patients accrue quality-of-life improvements immediately upon starting treatment	Likely inappropriate, as treatment takes time to exert its effects (per CADTH CDR clinical expert and as evidenced in UNCOVER-3, in which the proportion of patients achieving PASI 75 increases linearly from week 0 to week 12).[5] CADTH CDR's preferred assumption was use of a linear utility gain over the course of the trial period.
Monotherapy followed by SoC	Likely inappropriate. In practice, multiple lines of treatment are used, as is combinational and rotational therapy. CADTH CDR acknowledges that the manufacturer's model included the option to model sequences of treatment. However, there is a paucity of evidence to guide preferred treatment

Assumption	Comment
	sequences, as confirmed by CADTH CDR's consulting clinical expert.
Equivalent withdrawal rates	Likely inappropriate, as differential withdrawal rates among biologic drugs have been observed in practice.[21,28] However, this is a conservative assumption for ixekizumab.
Follow-up and monitoring schedule	The amount of follow-up necessary for biologics was underestimated (manufacturer's base case assumed one yearly visit, whereas two yearly visits are more likely, per CADTH CDR's clinical expert). Further, assumptions about chest X-rays likely overestimate the resource use needed for biologic drugs and do not reflect clinical practice. However, these assumptions had minimal impact on cost-effectiveness results.

CDR = Common Drug Review; PASI = Psoriasis Area and Severity Index.

Manufacturer's results

The manufacturer reported that, when compared with SoC, ixekizumab has an incremental cost-utility ratio (ICUR) of $113,023 per quality-adjusted life-year (QALY). When considering all the comparators using a sequential analysis, subsequent entry biologic (SEB) infliximab is associated the lowest ICUR ($85,983 per QALY versus SoC), followed by ixekizumab ($346,946 per QALY versus SEB infliximab). All other comparator drugs were either dominated or extendedly dominated.

TABLE 9: MANUFACTURER'S BASE-CASE RESULTS

	Total Costs	Total QALYs	Compared With SoC			Sequential ICUR ($/QALY)
			Incremental Cost (CAD)	Incremental QALYs	ICUR ($/QALY)	
SoC	$18,364	0.96	Reference			
Adalimumab	$60,316	1.35	$41,952	0.39	$109,914	Extendedly dominated by SoC and SEB infliximab
Etanercept	$62,503.02	1.31	$44,138.96	0.35	$128,812.88	Dominated by adalimumab
SEB infliximab	$66,526.16	1.53	$48,162.10	0.57	$85,983.49	$85,983
Ustekinumab 45 mg	$72,786.96	1.44	$54,422.90	0.48	$113,409.35	Dominated by SEB infliximab
Ustekinumab 90 mg	$75,453.58	1.47	$57,089.52	0.51	$112,040.68	Dominated by SEB infliximab
Secukinumab	$87,006.72	1.54	$68,642.66	0.58	$120,413.19	Extendedly dominated by SEB infliximab and ixekizumab
Ixekizumab	**$88,989.85**	**1.59**	**$70,625.79**	**0.63**	**$113,023.16**	**$346,946**

	Total Costs	Total QALYs	Compared With SoC			Sequential ICUR ($/QALY)
			Incremental Cost (CAD)	Incremental QALYs	ICUR ($/QALY)	
Infliximab	$111,983.49	1.53	$93,619.43	0.57	$167,138.16	Dominated by SEB infliximab

CAD = Canadian dollars; ICUR= Incremental cost-utility ratio; QALY =quality-adjusted life-year; SEB = subsequent-entry biologic; SoC = standard of care.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the text most effective strategy.
Source: Manufacturer's pharmacoeconomic submission.[3]

CADTH Common Drug Review Reanalyses

TABLE 10: CADTH COMMON DRUG REVIEW BASE-CASE RESULTS

	Total Costs	Total QALYs	Compared With SoC			Sequential ICUR ($/QALY)
			Incremental Cost (CAD)	Incremental QALYs	ICUR ($/QALY)	
SoC	$8,756	0.46	Reference			
Adalimumab	$48,281	0.80	$39,525	0.34	$117,480	Extendedly dominated by SoC and SEB infliximab
Etanercept	$50,545	0.76	$41,789	0.30	$138,809	Dominated by adalimumab
SEB infliximab	$54,168	0.96	$45,413	0.50	$91,064	$91,064
Ustekinumab 45 mg	$60,049	0.88	$51,294	0.42	$122,722	Dominated by SEB infliximab
Ustekinumab 90 mg	$62,534	0.90	$53,779	0.44	$120,934	Dominated by SEB infliximab
Secukinumab	$73,419	0.97	$68,642.66	0.51	$127,357	Extendedly dominated by SEB infliximab and ixekizumab
Ixekizumab	**$75,439**	**1.02**	**$70,625.79**	**0.56**	**$119,564**	**$360,307**
Infliximab	$96,958	0.96	$93,619.43	0.50	$176,869	Dominated by SEB infliximab

CAD = Canadian dollars; ICUR= Incremental cost-utility ratio; QALY =quality-adjusted life-year; SEB = subsequent-entry biologic; SoC = standard of care.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the text most effective strategy.

TABLE 11: CADTH COMMON DRUG REVIEW BASE-CASE RESULTS – PATIENTS WHO HAVE PREVIOUSLY EXPERIENCED TREATMENT FAILURE OF A BIOLOGIC DRUG

	Total Costs	Total QALYs	Compared With SoC			Sequential ICUR ($/QALY)
			Incremental Cost (CAD)	Incremental QALYs	ICUR ($/QALY)	
SoC	$8,756	0.46	Reference			
Adalimumab	$37,905	0.69	$29,149	0.23	$125,150	Extendedly dominated by SoC and SEB infliximab
Etanercept	$40,514	0.67	$31,758	0.21	$152,553	Dominated by adalimumab
SEB infliximab	$42,361	0.81	$33,605	0.35	$97,042	$97,042
Ustekinumab 45 mg	$47,026	0.75	$38,270	0.29	$132,060	Dominated by SEB infliximab
Ustekinumab 90 mg	$48,755	0.77	$39,999	0.31	$129,655	Dominated by SEB infliximab
Secukinumab	$56,529	0.81	$47,773	0.35	$135,485	Extendedly dominated by SEB infliximab and ixekizumab
Ixekizumab	**$58,595**	**0.85**	**$49,839**	**0.39**	**$128,612**	**$393,762**
Infliximab	$73,951	0.81	$65,196	0.35	$188,270	Dominated by SEB infliximab

CAD = Canadian dollars; ICUR= Incremental cost-utility ratio; QALY =quality-adjusted life-year; SEB = subsequent-entry biologic; SoC = standard of care.
Note: An extendedly dominated strategy has an ICUR higher than that of the next most effective strategy; therefore, an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the text most effective strategy.

Price-Reduction Analyses

TABLE 12: CADTH COMMON DRUG REVIEW PRICE-REDUCTION ANALYSES: IXEKIZUMAB VERSUS STANDARD OF CARE

ICURs of Ixekizumab Versus SoC			
Price	Base-case Analysis Submitted by Manufacturer	Reanalysis by CADTH CDR (Biologic-Naive Base Case)	CADTH CDR (Biologic-Experienced)
Base case ($1,519/80 mg injection)	$113,023	$119,451	$128,612
10% reduction ($1,367.10)	$101,127	$106,996	$115,123
25% reduction ($1,139.25)	$83,282	$88,145	$94,889
30% reduction ($1,063.30)	$77,335	$81,861	$88,145
35% reduction ($987.35)	$71,387	$75,577	$81,400
40% reduction ($911.40)	$65,439	$69,293	$74,656
45% reduction ($835.45)	$59,490	$63,010	$67,911
50% reduction ($759.50)	$53,542	$56,726	$61,167
55% reduction ($683.55)	$47,594	$50,442	$54,422
60% reduction ($607.60)	$41,646	$44,158	$47,678

CDR = Common Drug Review; ICUR = incremental cost-utility ratio; SoC = standard of care.

TABLE 13: CADTH COMMON DRUG REVIEW PRICE-REDUCTION ANALYSIS: IXEKIZUMAB VERSUS SUBSEQUENT ENTRY BIOLOGIC INFLIXIMAB

ICURs of Ixekizumab Versus SEB Infliximab			
Price	Base-case Analysis Submitted by Manufacturer	Reanalysis by CADTH CDR (Biologic-Naive Base Case)	CADTH CDR (Biologic-Experienced)
Base case ($1,519/80 mg injection)	$346,946	$360,307	$393,762
10% reduction ($1,367.10)	$232,135	$241,577	$266,978
25% reduction ($1,139.25)	$59,918	$63,481	$76,803
30% reduction ($1,063.30)	$2,513	$4,116	$13,411

CDR = Common Drug Review; ICUR = incremental cost-utility ratio; SEB = subsequent-entry biologic; SoC = standard of care.

PASI-to-Utility Mapping Algorithms

TABLE 14: ALTERNATIVE PASI-TO-UTILITY MAPPINGS — CADTH COMMON DRUG REVIEW BASE CASE

Mapping Algorithm	Utility Gain by PASI Score	ICUR for Manufacturer's Base Case (IXE Versus SoC, $/QALY)	ICUR for CADTH CDR Base Case (IXE Versus SoC, $/QALY)	ICUR for CADTH CDR Base Case, Biologic-Experienced (IXE Versus SoC, $/QALY)
Manufacturer's base case (Pan et al. 2011)[38]	PASI 90 to 100: 0.250 PASI 75 to 89: 0.220 PASI 50 to 74: 0.170 PASI < 50: 0.040	$113,026	$119,451	$128,612
Anis et al. 2011[39]	PASI 90 to 100: 0.21 PASI 75 to 89: 0.12 PASI 50 to 74: 0.12 PASI < 50: 0.04	$148,238	$157,034	$168,995
Woolacott et al. 2007[40]	PASI 90 to 100: 0.21 PASI 75 to 89: 0.19 PASI 50 to 74: 0.17 PASI < 50: 0.05	$149,835	$159,552	$172,121
Knight et al. 2012[41]	PASI 90 to 100: 0.232 PASI 75 to 89: 0.232 PASI 50 to 74: 0.201 PASI < 50: 0.101	$178,967	$194,509	$211,783

ICUR = incremental cost-utility ratio; IXE = ixekizumab; PASI = Psoriasis Area and Severity Index; QALY = quality-adjusted life-year; SoC = standard of care.

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