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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Ixekizumab (Taltz)

(Eli Lilly Canada Inc.)

Indication: Treatment of adult patients with active psoriatic arthritis who have responded inadequately to, or are intolerant to one or more disease-modifying antirheumatic drugs (DMARD). Taltz can be used alone or in combination with a conventional DMARD (e.g., methotrexate).

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	August 2018
Report Length:	40 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

ACR	American College of Rheumatology
BSC	best supportive care
CDR	CADTH Common Drug Review
DMARD	disease-modifying antirheumatic drug
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
HAQ-DI	Health Assessment Questionnaire–Disability Index
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
IL-17	interleukin-17
ITT	intention-to-treat population
NMA	network meta-analysis
PASI	Psoriasis Area and Severity Index
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
QALY	quality-adjusted life-year

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Ixekizumab (Taltz)
Study Question	From the perspective of the publicly funded health care payer, what is the incremental cost-effectiveness of ixekizumab, used alone or in combination with a conventional disease-modifying antirheumatic drug (DMARD), compared with conventional therapies in adult patients with active psoriatic arthritis (PsA) who have responded inadequately to or are intolerant to one or more conventional DMARDs?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with active PsA who have responded inadequately to or are intolerant to one or more conventional DMARDs who are: • biologic-naive or • biologic-experienced
Treatment	Ixekizumab, alone or in combination with a conventional DMARD, at the Health Canada–approved dosing regimen of 160 mg SC at week 0, followed by 80 mg every 4 weeks
Outcome	QALYs
Comparators	BSC, defined as the use of conventional DMARDS: methotrexate, lefluomide, or sulfasalazine Biologic drugs: adalimumab, apremilast, biosimilar infliximab, certolizumab pegol, etanercept 25 mg or 50 mg, golimumab, infliximab, secukinumab 150 mg or 300 mg, ustekinumab 45 mg or 90 mg
Perspective	Canadian public health care payer
Time Horizon	Lifetime (48 years in the base case)
Results for Base Case	• Biologic-naive: ICUR for ixekizumab vs. BSC was $65,815 per QALY gained. • Biologic-experienced: ICUR for ixekizumab vs. BSC was $53,593 per QALY gained. • In a sequential deterministic analysis, considering all comparators: o Ixekizumab was dominated (i.e., higher costs and lower effectiveness) by secukinumab 150 mg in both the biologic-naive and biologic-experienced populations.
Key Limitations	• Comparative efficacy of ixekizumab was based on an NMA with several limitations. The quality of the NMA was unclear given the limited reporting with respect to heterogeneity between studies and by the fact that comparative treatment efficacy in the economic model was informed by fixed-effects models that had poorer model fit. As such, the comparative efficacy of ixekizumab to BSC and biologics is uncertain for both biologic-naive and biologic-experienced populations. • The manufacturer estimated health utilities from EQ-5D-3L (a poorer fit model) converted from the more sensitive EQ-5D-5L version that was collected as part the SPIRIT trials. This resulted in less precise estimates in the utilities calculation. • There is uncertainty in the assumptions relating to disease progression after treatment discontinuation on biologics.

Key Limitations	• The manufacturer assumed no treatment response with BSC (i.e., conventional DMARDs alone). In the placebo arms of the clinical trials, patients were permitted to remain on concomitant conventional DMARDs in which 32.5% and 20.3% of patients reported a response on PsARC in SPIRIT-P1 and SPIRIT-P2, respectively. The NMA similarly reported treatment response in the placebo arm. The assumption of no treatment response for conventional DMARDs with respect to PsARC, PASI, or HAQ-DI resulted in an underestimation of the clinical effects of conventional DMARDs alone and, thereby, overestimated the difference in relative effectiveness between biologic treatment and BSC. • Uncertainty exists as to the long-term treatment effect of ixekizumab. Comparative clinical evidence for ixekizumab was available up to 24 weeks, but a very large proportion of placebo patients in the SPIRIT trials discontinued randomized treatment before week 24 (either due to early escape or because of treatment discontinuation), and claims of efficacy at week 24 are uncertain. • Given a number of different possible biologic treatments, ixekizumab could be used at different sequences in the treatment pathway; however, there is little evidence about the effect of different sequences of treatments. • The submitted model was not sufficiently flexible. Pairwise comparisons could be conducted probabilistically whereas sequential analyses that would involve considering more than two comparators could not be conducted probabilistically due to errors in the model code.
CDR Estimates	The CDR base-case reanalysis used utility values based on EQ-5D-5L from the overall ITT population that was associated with better fit statistics, considered a more conservative assumption about the rebound effect after biologic treatment discontinuation, and incorporated effectiveness for BSC as reported in the NMA. Based on these revisions, CDR found (based on deterministic analysis): • Ixekizumab was dominated by secukinumab 150 mg in both the biologic-naive and biologic-experienced populations (ixekizumab is associated with greater total costs and fewer QALYs). • A price reduction of 63% would be required for ixekizumab to be considered cost-effective at a $50,000 per QALY threshold in either population.

BSC = best supportive care; CDR = CADTH Common Drug Review; DMARD = disease-modifying antirheumatic drug; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HAQ-DI = Health Assessment Questionnaire–Disability Index; ICUR = incremental cost-utility ratio; ITT = intention-to-treat; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; QALY = quality-adjusted life-year; SC = subcutaneous; vs. = versus.

Drug	Ixekizumab (Taltz)
Indication	Indicated for the treatment of adult patients with active psoriatic arthritis who have responded inadequately to or are intolerant to one or more disease-modifying antirheumatic drugs (DMARD). Taltz can be used alone or in combination with a conventional DMARD (e.g., methotrexate).
Reimbursement Request	To be reimbursed for the treatment of adult patients with active psoriatic arthritis, used alone or in combination with methotrexate, when the response to previous conventional DMARDs therapy has been inadequate.
Dosage Form	Pre-filled syringe or autoinjector, 80 mg/mL.
NOC date	March 29, 2018
Manufacturer	Eli Lilly Canada Inc.

Executive Summary

Background

Ixekizumab (Taltz) is indicated for use in adult patients with active psoriatic arthritis (PsA) who have responded inadequately to or are intolerant to one or more conventional disease-modifying antirheumatic drugs (DMARDs). Ixekizumab can be used alone or in combination with a conventional DMARD.1 The dosage form is 80 mg/mL solution in a pre-filled syringe or pen, intended for patients to self-administer subcutaneously. The recommended dose for adult PsA patients or PsA patients with coexistent mild plaque psoriasis is an initial dose of 160 mg (two 80 mg injections), followed by 80 mg given every four weeks. For PsA patients with coexistent moderate to severe plaque psoriasis, the dosing regimen for plaque psoriasis should be used (initial dose of 160 mg [two 80 mg injections], followed by 80 mg given every other week until week 12 and then every four weeks thereafter).1 At the manufacturer's submitted price of $1,544.82 per 80 mg dose,1 the first-year cost of ixekizumab is $21,627 in patients with PsA or PsA patients with coexistent mild plaque psoriasis and $26,262 in PsA patients with coexistent moderate to severe plaque psoriasis; thereafter, the annual maintenance cost of ixekizumab is $20,138 per patient.

Ixekizumab was previously reviewed by CADTH in 2016 for the indication of moderate to severe plaque psoriasis. CADTH's Canadian Drug Expert Committee recommended listing ixekizumab with clinical criteria as follows: limited to patients with a documented inadequate response, contraindication, or intolerance to conventional systemic therapies such as methotrexate and cyclosporine, and treatment should be discontinued if a response to treatment with ixekizumab has not been demonstrated after 12 weeks.[2] The manufacturer's submitted price for ixekizumab at the time of this CADTH Common Drug Review (CDR) submission was $1,519 per 80 mg dose.

The manufacturer submitted a cost-utility analysis of ixekizumab compared with best supportive care (BSC) and biologics in patients with active PsA whose disease was not adequately controlled or who were intolerant to one or more conventional DMARDs. BSC was defined as conventional DMARDs, which included methotrexate, sulfasalazine, and

leflunomide.[1] The analysis was done separately for a biologic-naive population and a biologic-experienced population. The analysis was conducted from the perspective of the Canadian publicly funded health care payer over a lifetime horizon (48 years), with future costs and benefits discounted at 1.5%.[1] The model structure included a short-term treatment trial period in which efficacy was modelled in terms of responder status (defined as an improvement in two of the four Psoriatic Arthritis Response Criteria [PsARC] based on the following four measures: patient-self assessment, physician assessment, joint pain/tenderness score, and joint swelling score, one of which is the joint pain/tenderness score or joint swelling score, with no worsening in any of these four measures) and a long-term maintenance phase consisting of three health states: on maintenance treatment with ixekizumab; on treatment with BSC; or death. In the maintenance phase, patients on ixekizumab may remain on treatment, discontinue ixekizumab and transition to BSC, or die. Patients on BSC were modelled as remaining on BSC until death.[1] The main clinical effectiveness data for ixekizumab were derived from two phase III placebo-controlled randomized clinical trials (SPIRIT-P1 and SPIRIT-P2 trials).[3,4] Efficacy inputs to the economic model were informed by a manufacturer-sponsored network meta-analysis (NMA)[5] that reported PsARC, Health Assessment Questionnaire–Disability Index (HAQ-DI) and Psoriasis Area and Severity Index (PASI). Treatment- and response-specific changes in HAQ-DI and PASI were used to estimate EuroQol 5-Dimensions questionnaire (EQ-5D) utility values through a regression mapping that was derived from the SPIRIT-P1 and SPIRIT-P2 trial results.[1,3,4] Patients who transitioned to BSC were assumed to experience disease progression as reflected by an increasing HAQ-DI score of 0.072 per year based on data about patients with inflammatory polyarthritis from the UK's Norfolk Arthritis Register.[1]

In the biologic-naive population, the manufacturer reported an incremental cost-utility ratio (ICUR) of $65,815 per quality-adjusted life-year (QALY) compared with BSC. Compared with BSC only, ixekizumab was associated with a 1% probability of being cost-effective at a $50,000 per QALY threshold.[1] In the biologic-experienced population, the manufacturer reported an ICUR of $53,593 per QALY compared with BSC. Compared with BSC only, ixekizumab had a 30% probability of being the most likely cost-effective intervention at a $50,000 per QALY threshold.[1] In a sequential analysis considering all biologic comparators, ixekizumab was found to be dominated (i.e., had higher costs and lower QALYs) by secukinumab 150 mg in both populations.

Summary of Identified Limitations and Key Results

CDR identified several key limitations with the model submitted by the manufacturer. First, estimates of the comparative clinical efficacy of ixekizumab compared with BSC and biologic treatments came from the manufacturer's NMA,[5] the results of which are uncertain. Second, a number of assumptions were required to derive the relationship between health utility values and HAQ-DI and PASI, and the selected set of assumptions resulted in a regression model with poorer fit.[1] Third, the manufacturer's submitted model assumed that the progression of arthritis as measured by the HAQ-DI score would rebound to the baseline values once patients withdrew from treatment. Limited information exists to inform how patients would progress once treatment is discontinued. [6] The manufacturer also assumed that there would be no treatment effect from taking conventional DMARDs despite the placebo arm of both trials reporting otherwise.[3,4] The clinical expert consulted in this CDR review did not consider this an appropriate assumption. In addition, it is unclear whether the efficacy of biologics would be maintained over the patient's lifetime while they remain on treatment, and the long-term efficacy of ixekizumab is not certain. A further difficulty with the model was that probabilistic analysis of multiple comparators required to conduct sequential

analysis was not possible. All sequential analyses are therefore deterministic, and uncertainty in parameter values could not be effectively captured. Of note, the difference between the deterministic and probabilistic ICURs was under $1,000 per QALY in both populations in the manufacturer's base case.

CDR attempted to address these limitations by conducting a reanalysis that selected a utility equation with better fit, assumed a more conservative rebound effect following discontinuation of a biologic, and included a treatment effect for BSC. In the CDR reanalysis, in both the biologic-naive and biologic-experienced populations, ixekizumab was dominated by secukinumab 150 mg (i.e., ixekizumab was associated with higher total costs and fewer QALYs).

Conclusions

In biologic-naive adult patients with active PsA who have responded inadequately to or are intolerant to one or more DMARDs, ixekizumab was dominated by secukinumab 150 mg in the CDR base-case reanalysis, indicating that the use of secukinumab 150 mg is associated with both lower total costs and more QALYs compared with ixekizumab. In considering all relevant comparators, for ixekizumab to have an ICUR fall below $50,000 per QALY, a price reduction of 63% would be required.

A similar conclusion could be drawn in biologic-experienced patients in which ixekizumab was dominated by secukinumab 150 mg. BSC was the optimal therapy if a decision-maker's cost-effectiveness threshold was less than $74,949 per QALY gained, and if the cost-effectiveness threshold was greater than $74,949, secukinumab 150 mg would be the optimal therapy. A price reduction of 63% would be required for the ICUR of ixekizumab to fall below $50,000 per QALY when considering all relevant comparators.

The CDR reanalyses assume that long-term treatment efficacy is consistent over time.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing the initiation of ixekizumab to best supportive care (BSC) and biologics indicated for the treatment of psoriatic arthritis (PsA) (i.e., adalimumab, apremilast, biosimilar infliximab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, and ustekinumab) in adult patients with active PsA who had responded inadequately to or are intolerant to one or more conventional disease-modifying antirheumatic drugs (DMARDs).[1] BSC was defined as a conventional DMARD, which included methotrexate, sulfasalazine, and leflunomide.[1] The model used a lifetime horizon from the perspective of the publicly funded health care payer with costs and clinical outcomes (quality-adjusted life-years, or QALYs) discounted at 1.5% per annum. The model reflected a population that had similar baseline characteristics to the SPIRIT-P1 and SPIRIT-P2 trials (51.8% males; mean age, 51 years; mean weight, 87 kg).[3,4] Baseline Health Assessment Questionnaire–Disability Index (HAQ-DI) values in the patient cohort were assumed to be 1.18 in the biologic-naive population and 1.25 in the biologic-experienced population.

The model structure included a short-term treatment trial period, a long-term continuous treatment period, and a BSC health state. The trial period was treatment specific and was based on the time frame of the primary end point in the respective phase III trials (i.e., 12 weeks for adalimumab, certolizumab pegol, and etanercept; 16 weeks for apremilast, golimumab, ixekizumab, and secukinumab; and 24 weeks for infliximab, biosimilar infliximab, and ustekinumab).[1] At the end of the treatment trial period, patients who had a treatment response (defined as an improvement in two of the four Psoriatic Arthritis Response Criteria [PsARC] based on the following four measures: patient-self assessment, physician assessment, joint pain/tenderness score, and joint swelling score, one of which is the joint pain/tenderness score or joint swelling score, with no worsening in any of these four measures) remained on treatment and entered the continuous treatment state until discontinuation.[1] It was assumed that 16.5% of patients discontinued biologics each year. Treatment response inputs in the economic model were obtained from the manufacturer's submitted network meta-analysis (NMA).[5] Patients remaining on treatment were assumed to have treatment-specific response in arthritis (as measured by the HAQ-DI) and skin (as measured by the Psoriasis Area and Severity Index [PASI]) and not to progress in symptoms while on continuous biologic treatment, reflecting an arrest in disease progression.[1] Patients on BSC were assumed to remain at baseline PASI and HAQ-DI scores. Nonresponders to biologic treatment or patients who withdrew from the continuous treatment state entered the BSC state. In patients who discontinued and entered the BSC health state, they were assumed to no longer receive efficacious treatment, and the HAQ-DI score was assumed to rebound by the same amount as the initial decrement observed at baseline.[1] It was further assumed that disease would progress with an increment in HAQ-DI score (i.e., constant increment of 0.072 per year in all patients on BSC, an assumption similarly taken by Rodgers et al. in a UK PsA economic model[6]). The continuous treatment phase was based on a Markov state-transition model with monthly cycles.[1]

Patients could die at any time according to age- and gender-specific Canadian mortality tables corrected for PsA standardized mortality ratio based on Canadian data of 1.36.[7] The manufacturer's model assumed no mortality effect of treatment; all treatment-benefits were captured by an improvement in the health-related quality of life (HRQoL).[1] HRQoL improvements in responders were treatment specific and were based on reductions in the HAQ-DI and PASI as reported from the manufacturer's NMA.[5] HRQoL values were estimated based on an ordinary least squares regression analysis in which EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) utilities (which were mapped from the EQ-5D-5L responses observed in the ixekizumab clinical trial program) were regressed on the trial's HAQ-DI and PASI scores .[1] The model assumed no decrement in utility due to adverse events. The model included drug acquisition, administration and monitoring costs, medical costs relating to HAQ-DI and PASI scores, and the costs of treating adverse events. Drug acquisition costs were from the Ontario Drug Benefit formulary[8] or IMS Brogan when necessary. Drug costs took into account recommended dosing schedules and titration, where appropriate, and reflected the dosing for patients with PsA only. Administration costs and monitoring costs were treatment specific. The model did not directly include drug costs for conventional DMARDs, as these were assumed to be captured in the annual medical costs based on algorithms that estimated health care costs based on absolute PASI and HAQ-DI scores, which were treatment specific. The equations to determine costs related to HAQ-DI and PASI were derived from a study that reported costs of treatment of rheumatoid arthritis patients in the UK and Sweden[9] and psoriasis patients in the United Kingdom[10] and Netherlands.[11] International costs were converted to Canadian dollars and updated to 2017.

Manufacturer's Base Case

In the biologic-naive population, the manufacturer's probabilistic analysis reported that ixekizumab was associated with an additional cost of $53,699 with a gain of 0.816 additional QALYs over the lifetime of patients compared with BSC. The resulting incremental cost-utility ratio (ICUR) was $65,815 per QALY gained when compared with BSC (Table 2).[1]

In biologic-experienced population, ixekizumab was found by the manufacturer to be $61,824 more expensive with an estimated benefit of 1.154 QALYs over the lifetime of patients compared with BSC with an associated ICUR of $53,593 per QALY in the probabilistic analysis (Table 3).[1]

Table 2: Summary of Results of the Manufacturer's Base Case for Biologic-Naive Patients

	Deterministic Results			Probabilistic Results		
	Ixekizumab (a)	BSC (b)	Difference (a − b)	Ixekizumab (d)	BSC (e)	Difference (d − e)
QALYs	13.79	13.00	0.80	NR	NR	0.816[a]
Costs ($)						
Treatment	63,253	0	63,253	NR	NR	
Administration	167	0	167	NR	NR	
Physician visits	1,048	0	1,048	NR	NR	
Monitoring	0	0	0	NR	NR	
Adverse event	0	0	0	NR	NR	
Health state, on Tx	10,185	0	10,185	NR	NR	
BSC	148,207	170,814	−22,608	NR	NR	
Total costs	222,859	170,814	52,044	NR	NR	53,699[a]
ICUR ($/QALY)			65,413			65,815[a]

BSC = best supportive care; ICUR = incremental cost-utility ratio; NR = not reported and not available in model; QALY = quality-adjusted life-year; Tx = treatment.
[a] Calculated from manufacturer model.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

Table 3: Summary of Results of the Manufacturer's Base Case for Biologic-Experienced Patients

	Deterministic Results			Probabilistic Results		
	Ixekizumab (a)	BSC (b)	Difference (a − b)	Ixekizumab (d)	BSC (e)	Difference (d − e)
QALYs	12.23	11.09	1.15	NR	NR	1.15[a]
Costs ($)						
Treatment	73,690	0	73,690	NR	NR	
Administration	194	0	194	NR	NR	
Physician visits	1,219	0	1,219	NR	NR	
Monitoring	0	0	0	NR	NR	
Adverse event	0	0	0	NR	NR	
Health state, on Tx	12,013	0	12,013	NR	NR	
BSC	145,461	172,102	−26,641	NR	NR	
Total costs	232,576	172,102	60,475	NR	NR	61,824[a]
ICUR ($/QALY)			52,780			53,593[a]

BSC = best supportive care; ICUR = incremental cost-utility ratio; NR = not reported and not available in model; QALY = quality-adjusted life-year; Tx = treatment.
[a] Calculated from manufacturer model.
Source: Manufacturer's Pharmacoeconomic Submission.[1]

CADTH Common Drug Review (CDR) reviewers recalculated the results sequentially in order to reflect recent CADTH guidelines[12] that, when multiple comparators are relevant, all should be considered in a sequential manner. A sequential analysis involves calculating the ICUR for a less costly comparator compared with the next most costly comparator, excluding all comparators that are either dominated or subjected to extended dominance.[12] As the manufacturer's model had coding errors that did not allow the model to run probabilistically, all sequential analyses reported henceforth are deterministic. In the sequential analysis of biologic-naive patients (Table 4), ixekizumab had higher costs and lower QALYs than secukinumab 150 mg (i.e., ixekizumab was dominated by secukinumab 150 mg). Biosimilar infliximab was found to be the optimal therapy at a cost-effectiveness threshold greater than or equal to $49,821 per QALY. In the sequential analysis of biologic-experienced patients (Table 5), ixekizumab had higher costs and lower QALYs than secukinumab 150 mg. From a cost-effectiveness threshold greater than $21,884 per QALY, secukinumab 150 mg would be considered the cost-effective treatment; if a decision-maker's cost-effectiveness threshold was below this value, BSC would be considered the cost-effective treatment.

Table 4: Sequential Incremental Cost-Effectiveness Ratio Analysis Results of the Manufacturer's Base Case in Biologic-Naive Patients (Deterministic Results)

Comparators	Total Costs ($)	Total QALYs	ICUR, Compared With BSC ($/QALY)	Sequential ICUR ($/QALY)
BSC	170,815	13.00	-	-
Secukinumab 150 mg	194,704	13.87	27,534	27,534
Biosimilar infliximab	233,275	14.25	49,783	99,656
Dominated Options				
Apremilast	199,782	13.59	49,106	Dominated
Certolizumab pegol	214,766	13.85	51,439	Dominated
Ixekizumab	222,859	13.79	65,375	Dominated
Adalimumab	224,210	13.81	65,901	Dominated
Secukinumab 300 mg	225,057	13.76	70,880	Dominated
Golimumab	237,059	14.05	62,975	Dominated
Etanercept 50 mg 2.q.w.	241,494	14.12	62,828	Dominated
Etanercept 25 mg 2.q.w.	242,326	14.12	63,567	Dominated

2.q.w. = twice weekly; BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer's Pharmacoeconomic Submission.[1]

Table 5: Sequential Incremental Cost-Effectiveness Ratio Analysis Results of the Manufacturer's Base Case in Biologic-Experienced Patients (Deterministic Results)

Comparators	Total Costs ($)	Total QALYs	ICUR, Compared With BSC ($/QALY)	Sequential ICUR ($/QALY)
BSC	172,102	11.09	-	-
Secukinumab 150 mg	197,987	12.27	21,884	21,884
Dominated Options				
Certolizumab pegol	220,360	12.23	42,116	Dominated
Secukinumab 300 mg	231,779	12.15	56,020	Dominated
Ixekizumab	232,576	12.23	52,780	Dominated

BSC = best supportive care; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer's Pharmacoeconomic Submission.[1]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using one-way deterministic sensitivity analyses, scenario analyses, and Monte Carlo simulation for probabilistic sensitivity analysis.[1] The majority of the manufacturer's sensitivity analyses focused on the comparison between ixekizumab and BSC; one sensitivity analysis was presented in which ixekizumab was compared with other biologic treatments.

Based on the manufacturer's reported sensitivity analyses, the results were most sensitive to the cost of ixekizumab for both the biologic-naive and the biologic-experienced population. In the biologic-naive population, the ICUR for ixekizumab compared with BSC varied from $49,541 per QALY (if pack costs decreased by 20% to $1,236) to $81,360 per QALY (if pack costs increased by 20% to $1,854). In the biologic-experienced population, the ICUR for ixekizumab compared with BSC ranged from $39,392 per QALY (reduced pack costs) to $65,643 per QALY (increased pack costs).[1]

Multiple scenario analyses were undertaken comparing ixekizumab to BSC. Specifically, the model was found to be sensitive to the following:

- Time horizon: The manufacturer tested a 10-year time horizon, which increased the ICURs of ixekizumab to $122,416 per QALY in the biologic-naive population and $87,881 per QALY in the biologic-experienced population when compared with BSC.[1]
- Rebound effect: In one scenario analysis, the manufacturer tested a scenario where, after discontinuing biologic treatment, the HAQ-DI score would return to where the HAQ-DI would have progressed if no biologic had been taken. This scenario increased the ICURs of ixekizumab compared with BSC in the biologic-naive and the biologic-experienced populations to $138,279 per QALY and $95,749 per QALY, respectively.[1] In a second scenario analysis, the manufacturer tested a scenario where, after discontinuing biologic treatment, some of the treatment effect on the HAQ-DI score remained. This scenario decreased the ICURs of ixekizumab compared with BSC in the biologic-naive and biologic-experienced populations to $29,490 per QALY and $25,151 per QALY, respectively.[1]
- Utility equations: A scenario using the utility equation based on EQ-5D-5L increased the ICURs to $80,220 per QALY and $68,968 per QALY for biologic-naive and biologic-experienced patients, respectively.

- Placebo effectiveness: The manufacturer reported that applying placebo efficacy to BSC and no HAQ-DI progression on BSC resulted in ICURs of $10,140 per QALY in the biologic-naive population and $11,082 per QALY in the biologic-experienced population. In a scenario where no placebo efficacy and no HAQ-DI progression were applied, there was an increase in ICUR in both populations: $227,054 per QALY for biologic-naive patients and $137,322 per QALY for biologic-experienced patients.

Limitations of Manufacturer's Submission

1. **Uncertain comparative effectiveness of ixekizumab compared with BSC and biologics:** Clinical efficacy inputs to the economic model in terms of PsARC, HAQ-DI, and PASI were informed by the manufacturer's submitted NMA.[5] The economic model incorporated the fixed-effects model from the NMA in which separate networks were provided for biologic-naive and biologic-experienced populations. Due to poor reporting, there was insufficient evidence provided to assess clinical heterogeneity between the included studies. However, in comparing the deviance information criterion between the random-effects and fixed-effects model (i.e., the lowest criterion is considered the better fit model), the NMA reported that, for some outcomes, the deviance information criterion was more than 5 points higher in the fixed-effects model compared with the random-effects model (see CDR Clinical Report). Selecting the clinical effectiveness outcomes from the fixed-effects model may limit the credibility of the clinical findings and leads to uncertainty in the comparative efficacy between treatment options that consequently impacts the uncertainty associated with the cost-effectiveness results from the economic model.

2. **Selection of the utility equation:** In the SPIRIT-P1 and SPIRIT-P2 trials,[3,4] EQ-5D-5L was collected to measure patients' health utility. The manufacturer then transformed the EQ-5D-5L to EQ-5D-3L using the mapping function developed by van Hout et al.[13] The EQ-5D-5L is the most recent iteration of the EQ-5D instrument and was developed to make up for the lack of sensitivity of the EQ-5D-3L by increasing the possible levels of severity in each of the five dimensions from 3 to 5.[14] It is unclear what the manufacturer's rationale was for transforming the EQ-5D-5L scores to an older EQ-5D-3L version.

   In the manufacturer's submitted base case, utility scores were modelled based on treatment- and response-specific changes in HAQ-DI and PASI values.[1] The association between utility values were estimated using an ordinary least squares regression model in which the manufacturer regressed EQ-5D-3L (mapped from EQ-5D-5L) on HAQ-DI and PASI data that were reported in the SPIRIT-P1 and SPIRIT-P2 trials. Separate ordinary least squares models were estimated in the biologic-naive (i.e., SPIRIT-P1) and biologic-experienced populations (i.e., SPIRIT-P2) from two sample populations: the "active treatment intention-to-treat" (ITT) population and the "overall ITT" population. The active treatment ITT population included all patients allocated to ixekizumab or adalimumab (i.e., patients on placebo were excluded) while the overall ITT population included all patients (i.e., patients on placebo were included).[1] The manufacturer claimed that the active treatment ITT population represented a more homogeneous patient population by only including patients allocated to ixekizumab or adalimumab. In the manufacturer's base case, the utility equation based on regressing ED-5D-3L onto HAQ-DI and PASI in the active treatment ITT population was selected to inform utility assignment.[1]

The adjusted R-squared was reported to assess the fit of the models. The models with the best fit in both the biologic-naive and biologic-experienced populations were those utility equations that regressed EQ-5D-5L from the overall ITT population.[1] These models were also preferred given that the EQ-5D-5L is meant to be more sensitive than the EQ-5D-3L. In the CDR reanalysis, utilities from EQ-5D-5L estimated in the overall ITT population were used as the utility equation.

3. **Uncertain assumptions regarding disease progression upon treatment discontinuation:** The manufacturer assumed that the progression of arthritis as measured by the HAQ-DI score would rebound to the baseline values when patients withdrew from treatment (i.e., HAQ-DI = 1.18 [biologic-naive] and 1.25 [biologic-experienced]). Limited information exists to inform how patients will progress when treatment is discontinued.[6] CDR considered the manufacturer's alternative scenario analysis, in which patients entering the BSC health state were assigned a HAQ-DI score that would have been expected if they had never received any treatment, to be more conservative and appropriate. Under such an assumption, patients would not maintain any of the initial improvement in HAQ-DI that was associated with treatment.

4. **No response on conventional DMARD:** In the manufacturer's base case no treatment effect was assumed from taking conventional DMARDs. This reflected the BSC arm of the model and, in the SPIRIT trials, this corresponded to the placebo arm, as patients on placebo were maintained on their existing conventional DMARDs. This assumption of no treatment efficacy on BSC seems unreasonable since the placebo arm of the SPIRIT-P1 trial reported a 32.1% response on PsARC (i.e., biologic-naive) and the placebo arm of the SPIRIT-P2 trial reported a 20.3% response at week 24 of treatment (i.e., biologic-experienced).[3,4] The clinical expert consulted in this CDR review did not consider this to be an appropriate assumption. In the CDR reanalysis, the treatment effects of placebo from the NMA were used to inform the treatment effect of BSC. The placebo treatment effect was captured as improvements in HAQ-DI, PASI, and PsARC.

5. **Uncertain long-term treatment efficacy:** The submitted model projected the analysis over a lifetime (i.e., 48 years) and assumed that treatment effects would be maintained over time (i.e., HAQ-DI and PASI values for treatment responders would remain constant). However, the available evidence on the efficacy of ixekizumab is limited to 24 weeks of double-blinded duration in which early escape was permitted after 16 weeks within the trials.[3,4] By week 24, only 85.8% and 80% of patients on placebo in the SPIRIT-P1 and SPIRIT-P2 trials, respectively, completed up to 24 weeks of randomized treatment, as the remainder exited the trial due to early escape or treatment discontinuation. Claims of efficacy at week 24 are therefore uncertain. Furthermore, according to the clinical expert consulted for this review, PsA is managed by a sequence of treatments. The assumption of lifetime use of BSC upon discontinuation of ixekizumab is therefore not appropriate, as patients are likely to be switched to another biologic after treatment failure due to poor response or adverse events according to the clinical expert. The manufacturer's model permitted exploration of treatment sequences, and CDR conducted exploratory analyses of different treatment sequence pathways to align with current economic guidelines to consider interventions in a broader space.[12]

6. **Deterministic sequential analyses:** The manufacturer's model was not sufficiently flexible to run probabilistic analysis in assessing all comparisons of interest sequentially. Probabilistic analysis is important to adequately address parameter

uncertainty.[12] CDR was unable to conduct a reanalysis probabilistically, and in the CDR reanalysis, all results are presented based on a deterministic model.

CADTH Common Drug Review Reanalyses

To account for the limitations identified above, CDR undertook several analyses as detailed below:

1. **Regression informing utility calculation:** EQ-5D-5L estimated from the overall ITT population was used to inform the regression analysis because it represented a better fit model.
2. **HAQ-DI rebound in patients withdrawing from active treatment:** HAQ-DI score rebounded to natural progression (i.e., after the biologic treatment was discontinued, the HAQ-DI score increased to the score it would have been had no biologic treatment been used) in patients who withdrew from active treatment and went to BSC. This approach was considered more conservative and was consistent with CDR's reanalysis of apremilast and ustekinumab for PsA.[15,16]
3. **Incorporating treatment response while on BSC:** NMA results from the placebo arm were applied to inform the treatment effectiveness of BSC treatment.[5]

CDR's base-case reanalysis entailed revising the model based on the three above-mentioned issues and correcting the price of apremilast. All CDR reanalyses were deterministic, as the manufacturer's model was not sufficiently flexible to permit evaluating all comparators of interest sequentially in a probabilistic analysis. Detailed results can be found in Appendix 5.

In the CDR reanalysis of the biologic-naive population, BSC is the cost-effective option at a cost-effectiveness threshold of less than $79,331 per QALY; secukinumab 150 mg is cost-effective if the decision-maker is willing to pay $79,331 per QALY and less than $165,717 per QALY; and biosimilar infliximab is cost-effective if the decision-maker is willing to pay more than $165,717 per QALY (Table 6).

Table 6: Results From CDR Base Case for Biologic-Naive Patient Population (Deterministic Results)

Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($/QALY)
Base Case Submitted by Manufacturer	BSC	13.00	170,815	
	Secukinumab 150 mg	13.87	194,704	27,534
	Biosimilar infliximab	14.25	233,275	99,656
	Apremilast	13.59	199,782	Dominated
	Certolizumab pegol	13.85	214,766	Dominated
	Ixekizumab q.4.w.	13.79	222,859	Dominated
	Adalimumab	13.81	224,210	Dominated
	Secukinumab 300 mg	13.76	225,057	Dominated
	Golimumab	14.05	237,059	Dominated
	Etanercept 50 mg 2.q.w.	14.12	241,494	Dominated
	Etanercept 25 mg 2.q.w.	14.12	242,326	Dominated
CDR Base-Case	BSC	14.57	156,221	

Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($/QALY)
Reanalysis	Secukinumab 150 mg	14.93	185,071	79,331
	Biosimilar infliximab	15.16	223,012	165,717
	Apremilast	14.77	187,791	Dominated
	Certolizumab pegol	14.91	205,052	Dominated
	Ixekizumab q.4.w.	14.91	212,754	Dominated
	Adalimumab	14.88	214,459	Dominated
	Secukinumab 300 mg	14.89	214,871	Dominated
	Golimumab	14.99	226,595	Dominated
	Etanercept 50 mg q.w.	15.05	232,947	Dominated
	Etanercept 25 mg 2.q.w.	15.05	233,778	Dominated

2.q.w. = twice weekly; BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; q.4.w. = every 4 weeks; q.w. = once weekly.

In the CDR reanalysis of the biologic-experienced population, BSC was the cost-effective option if the decision-maker is willing to pay $74,949 per QALY; and secukinumab 150 mg is cost-effective if the decision-maker is willing to pay more than $74,949 per QALY (Table 7).

Exploratory analyses were conducted to investigate ixekizumab at different lines of therapy using the CDR base-case model. Details on the methods and results can be found in Appendix 5.

A price reduction analysis was undertaken to determine at what price ixekizumab would have to be in order to be considered cost-effective at $50,000 per QALY. In the CDR base case, the price at which ixekizumab would be considered cost-effective at a $50,000 per QALY threshold was 63% lower for both the biologic-naive and the biologic-experienced populations (Table 8).

Table 7: Results From CDR Base Case for Biologic-Experienced Patient Population (Deterministic Results)

Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($/QALY)
Base Case Submitted by Manufacturer	BSC	11.09	172,102	
	Secukinumab 150 mg	12.27	197,987	21,884
	Certolizumab pegol	12.23	220,360	Dominated
	Secukinumab 300 mg	12.15	231,779	Dominated
	Ixekizumab q.4.w.	12.23	232,576	Dominated
CDR Base Case Reanalysis	BSC	14.30	154,560	
	Secukinumab 150 mg	14.72	186,248	74,949
	Certolizumab pegol	14.70	208,523	Dominated
	Secukinumab 300 mg	14.68	219,469	Dominated
	Ixekizumab q.4.w.	14.71	220,639	Dominated

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; q.4.w. = every 4 weeks.

Table 8: CDR Reanalysis Price Reduction Scenarios

ICURs of Submitted Drug Versus All Available Psoriatic Arthritis Treatments		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
Biologic-Naive Population		
Submitted	If λ < $27,534, BSC is optimal If $27,534 < λ < $99,656, secukinumab 150 mg is optimal If λ > $99,656, biosimilar infliximab mg is optimal	If λ < $79,331, BSC is optimal If $79,331 < λ < $165,717 secukinumab 150 mg is optimal If λ > $165,717, biosimilar infliximab mg is optimal
10% reduction	If λ < $27,534, BSC is optimal If $27,534 < λ < $99,656, secukinumab 150 mg is optimal If λ > $99,656, biosimilar infliximab mg is optimal	If λ < $79,331, BSC is optimal If $79,331 < λ < $165,717 secukinumab 150 mg is optimal If λ > $165,717, biosimilar infliximab mg is optimal
20% reduction	If λ < $27,534, BSC is optimal If $27,534 < λ < $99,656, secukinumab 150 mg is optimal If λ > $99,656, biosimilar infliximab mg is optimal	If λ < $79,331, BSC is optimal If $79,331 < λ < $165,717 secukinumab 150 mg is optimal If λ > $165,717, biosimilar infliximab mg is optimal
30% reduction	If λ < $27,534, BSC is optimal If $27,534 < λ < $99,656, secukinumab 150 mg is optimal If λ > $99,656, biosimilar infliximab mg is optimal	If λ < $79,331, BSC is optimal If $79,331 < λ < $165,717 secukinumab 150 mg is optimal If λ > $165,717, biosimilar infliximab mg is optimal
40% reduction	If λ < $27,534, BSC is optimal If $27,534 < λ < $99,656, secukinumab 150 mg is optimal If λ > $99,656, biosimilar infliximab mg is optimal	If λ < $79,331, BSC is optimal If $79,331 < λ < $165,717 secukinumab 150 mg is optimal If λ > $165,717, biosimilar infliximab mg is optimal
50% reduction	If λ < $25,648, BSC is optimal **If $25,648 < λ < $48,536, ixekizumab is optimal** If $48,536 < λ < $99,656, secukinumab 150 mg is optimal If λ > $99,656, biosimilar infliximab mg is optimal	If λ < $73,201, BSC is optimal If $73,201 < λ < $165,717, ixekizumab is optimal If λ > $165,717, biosimilar infliximab is optimal
60% reduction	If λ < $17,702, BSC is optimal If $17,702 < λ < $105,478, ixekizumab is optimal If λ > $105,478, biosimilar infliximab mg is optimal	If λ < $54,611, BSC is optimal If $54,611 < λ < $191,028, ixekizumab is optimal If λ > $191,028, biosimilar infliximab is optimal

ICURs of Submitted Drug Versus All Available Psoriatic Arthritis Treatments		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
70% reduction	If λ < $9,757, BSC is optimal If $9,757 < λ < $119,272, ixekizumab is optimal If λ > $119,272, biosimilar infliximab mg is optimal	If λ < $36,021, BSC is optimal **If $36,021 < λ < $216,092, ixekizumab is optimal** If λ > $216,092 biosimilar infliximab is optimal
Biologic-Experienced Population		
Submitted	If λ < $21,884, BSC is optimal If λ > $21,884, secukinumab 150 mg is optimal	If λ < $74,949, BSC is optimal If λ > $74,949, secukinumab 150 mg is optimal
10% reduction	If λ < $21,884, BSC is optimal If λ > $21,884, secukinumab 150 mg is optimal	If λ < $74,949, BSC is optimal If λ > $74,949, secukinumab 150 mg is optimal
20% reduction	If λ < $21,884, BSC is optimal If λ > $21,884, secukinumab 150 mg is optimal	If λ < $74,949, BSC is optimal If λ > $74,949, secukinumab 150 mg is optimal
30% reduction	If λ < $21,884, BSC is optimal If λ > $21,884, secukinumab 150 mg is optimal	If λ < $74,949, BSC is optimal If λ > $74,949, secukinumab 150 mg is optimal
40% reduction	If λ < $21,884, BSC is optimal If λ > $21,884, secukinumab 150 mg is optimal	If λ < $74,949, BSC is optimal If λ > $74,949, secukinumab 150 mg is optimal
50% reduction	If λ < $20,623, BSC is optimal **If $20,623 < λ < $60,830, ixekizumab optimal** If λ > $60,830, secukinumab 150 mg is optimal	If λ < $70,412, BSC is optimal If $70,412 < λ < $322,324, secukinumab 150 mg is optimal If λ > $322,324, secukinumab 150 mg is optimal
60% reduction	If λ < $14,192, BSC is optimal If $14,192 < λ < $259,566, ixekizumab optimal If λ > $259,566, secukinumab 150 mg is optimal	If λ < $52,663, BSC is optimal If $52,663 < λ < $1,290,039, ixekizumab is optimal If λ > $1,290,039, secukinumab 150 mg is optimal
70% reduction	If λ < $7,761, BSC is optimal If $7,761 < λ < $458,303, ixekizumab optimal If λ > $458,303, secukinumab 150 mg is optimal	If λ < $34,915, BSC is optimal **If $34,915 < λ < $2,257,755, ixekizumab is optimal** If λ > $2,257,755, secukinumab 150 mg is optimal

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

Issues for Consideration

- The clinical expert consulted as part of this CDR review reported that PsARC is not typically used in clinical practice to define responders, although this was the outcome used in the model. Rather, the clinical expert noted that ACR20 (20% American College of Rheumatology response, defined as an improvement of at least 20% in both swollen and tender joint counts and at least three of five additional disease criteria) may be a more appropriate definition of responder in PsA. The clinical data from the trials suggest a correlation between ACR20 and PsARC results, although, given the structure of the manufacturer's model, it was not possible to run an analysis in which response was defined solely based on ARC20.[3,4]
- According to the clinical expert consulted as part of this CDR review, there is uncertainty about the place in therapy for ixekizumab in clinical practice. There are a number of comparators including five original tumour necrosis factor inhibitors and at least two biosimilar tumour necrosis factor inhibitors, apremilast and an interleukin-17 (IL-17) inhibitor, secukinumab. The clinical expert further noted that ixekizumab is unlikely to be more effective for PsA patients with enthesitis, dactylitis, sacroilitis, or spondylitis.
- As per the clinical review, it remains unclear the role of IL-17 inhibitors in precipitating inflammatory bowel disease or uveitis in patients without an existing disease history. The clinical expert consulted as part this CDR review noted that measurement of fecal

calprotectin, colonoscopy, and video capsule endoscopy are being considered in order to identify patients in whom not to prescribe IL-17 inhibitors such as ixekizumab.

- Since 2017, two biosimilars of etanercept have become available in Canada.[17,18] Etanercept subsequent entry biologics are currently not approved for PsA (indication is for ankylosing spondylitis and moderately to severely active rheumatoid arthritis). The potential introduction of these comparators may affect the findings predicted by the economic analysis.

Patient Input

Input was received from the following patient groups: Arthritis Consumer Experts; The Arthritis Society and Canadian Arthritis Patient Alliance; The Canadian Spondylitis Association; and the Canadian Skin Patient Alliance, Canadian Association of Psoriasis Patients, and the Canadian Psoriasis Network. Patients emphasized that the impacts of PsA negatively impact all aspects of their lives. The symptoms with the greatest impact were reported to be pain, stiffness, fatigue, movement, skin sensitivity and appearance, and depression. Patients reported that overall quality of life is impacted through reduced social activities. The EQ-5D, which was the health outcome measure used in the economic analysis, measures dimensions of pain, depression, mobility, usual activities, and self-care, most of which were mentioned by patients.

Patients also reported the impact of flares, which were described as being incapacitating for some. Flares are reported as being unpredictable in terms of how bad they will be and how long they will last. The manufacturer's model did not include the cost or health consequences of flares. This may be important to consider in the cost-effectiveness analysis if there are any expected differences in flares between treatments.

Patients described having used many different treatments with different levels of success. It was stated that treatments were successful initially but became ineffective after a few years. As noted, there are limited long-term data on the treatment effect of ixekizumab beyond 24 weeks of treatment, and this comment from patients indicates that the efficacy of biologic treatment may not be maintained over time as assumed in the manufacturer's submitted model. This supports the need to consider the cost-effectiveness specific to biologic-naive and biologic-experienced patients separately, as reported in the manufacturer's submission. It further highlights the importance of considering the potential cost-effectiveness of ixekizumab in the context of its use as part of a sequence of treatments.

Conclusions

The CDR base case addressed several of the identified limitations with the manufacturer's model by selecting a utility equation with better fit, assuming a more conservative rebound effect following discontinuation of a biologic, and including a treatment effect for BSC. In considering ixekizumab compared with all relevant comparators (i.e., biologics and BSC) through sequential analyses, ixekizumab was not found to be cost-effective when considering all available treatments for patients with PsA, regardless of a decision-maker's willingness to pay in both biologic-naive and biologic-experienced patients.

In biologic-naive patients with active PsA who have responded inadequately to or are intolerant to one or more DMARDs, ixekizumab was dominated by secukinumab 150 mg in the CDR base-case reanalysis, indicating that the use of secukinumab 150 mg is associated with both lower total costs and more QALYs compared with ixekizumab. For ixekizumab to

not be dominated but to have an ICUR fall below $50,000 per QALY compared against all relevant comparators, a price reduction of 63% would be required. A similar conclusion was drawn for biologic-experienced patients. Ixekizumab was dominated by secukinumab 150 mg, and a price reduction of 63% would be required for the ICUR of ixekizumab to fall below $50,000 per QALY when compared with all relevant comparators.

Given that the manufacturer's model could not be conducted probabilistically with all comparators of interest, CDR notes that it is unclear to what extent parameter uncertainty could have impacted these results. The CDR reanalysis further assumed that long-term treatment efficacy remains consistent over time.

Appendix 1: Cost Comparison

The comparators presented in Table 9 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 9: CDR Cost Comparison Table for Psoriatic Arthritis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Ixekizumab (Taltz)	**80 mg**	**Pre-filled syringe or pen**	**1,544.8200[a]**	**160 mg SC at week 0, followed by 80 mg every 4 weeks[b]** **160 mg SC at week 0, followed by 80 mg weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks[c]**	**First year: 21,627 to 26,262** **Subsequent: 20,138**
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	769.9700	40 mg every other week SC injection	20,074
Certolizumab pegol (Cimzia)	200 mg/mL	Single-use pre-filled syringe	664.5100	400 mg SC injection at weeks 0, 2, and 4, then 200 mg every 2 weeks or 400 mg every 4 weeks	First year: 18,606 Subsequent: 17,325
Etanercept (Enbrel)	25 mg/vial	Vial	202.9300	50 mg weekly (one 50 mg injection or two 25 mg injections on the same day or 3 or 4 days apart)	21,163
	50 mg/mL	Pre-filled syringe or autoinjector	405.9850		21,169
Golimumab SC (Simponi)	50 mg/0.5 mL	Pre-filled syringe or autoinjector	1,555.1700	50 mg SC injection once a month (on the same date)	18,662
Infliximab (Remicade)	100 mg/vial	Vial	987.5600	5 mg/kg initial dose followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter	First year: 39,502[d] Subsequent: 32,184[d]
SEB Infliximab (Inflectra)	100 mg/vial	Vial	525.0000		First year: 21,000[d] Subsequent: 17.109[d]
SEB Infliximab (Renflexis)	100 mg/vial	Vial	525.0000[e]		First year: 21,000[d] Subsequent: 17,109[d]
Secukinumab (Cosentyx)	150 mg/mL	Pre-filled syringe, pen, or vial	822.5000	150 mg SC at weeks 0, 1, 2, 3, and 4 followed by monthly thereafter	First year: 13,160 Subsequent: 9,870
Ustekinumab (Stelera)	45 mg/0.5 mL 90 mg/mL	Pre-filled syringe or vial	4,593.1400 4,593.1400	Patients < 100 kg: 45 mg at weeks 0 and 4, then every 12 weeks thereafter Patients > 100 kg: 90 mg at weeks 0 and 4, then every 12 weeks thereafter	First year: 22,966 Subsequent: 19,958
Phosphodiesterase Type 4 Inhibitors					
Apremilast (Otezla)	10 mg 20 mg 30 mg	Tablet	18.9041[f]	30 mg twice daily, following titration	13,800

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Disease-Modifying Antirheumatic Drugs					
Methotrexate (generics)	2.5 mg 10 mg 10 mg/mL 25mg/mL	Tablet Tablet Injection Injection	0.6325 2.6505[g] 12.5000/2 mL 8.9200/2 mL	7.5 mg to 25 mg per week until response achieved; dose adjusted to optimal clinical response; 30 mg/week not ordinarily exceeded	Oral up to $396 (assuming 30 mg dose per week, 2.5 mg tabs)
Leflunomide (generics)	10 mg 20 mg	Tablet	2.6433 2.6433	Loading: 100 mg daily for 3 days Maintenance: 20 mg daily	First year: 997 Subsequent: 965
Sulfasalazine (generics)	500 mg 500 mg	Tablet EC tablet	0.1804 0.2816	Titration: Week 1: 500 mg/day Week 2: 1,000 mg/day Week 3: 1,500 mg/day Maintenance: 2,000 mg/day	Reg tabs First year: 256 Subsequent: 263 EC tabs First year: 399 Subsequent: 411

CDR = CADTH Common Drug Review; EC = enteric coated; PsA = psoriatic arthritis; SC = subcutaneous; SEB = subsequent entry biologic.
Note: All prices are from the Ontario Drug Benefit Formulary and Employee Assistance Program (accessed Mar 2018)[8] unless otherwise indicated and do not include dispensing fees. First year is assumed to be 52 weeks long (364 days), while subsequent years are 365 days. Products without a distinct initiation phase are reported as cost per 365-day year.
[a] Manufacturer's submitted price.[1]
[b] Dosing regimen for adult PsA patients or PsA patients with coexistent mild plaque psoriasis.
[c] Dosing regimen for adult PsA patients with coexistent moderate to severe plaque psoriasis.
[d] Assumes patient weight of 87 kg (five 100 mg vials, with wastage) based on SPIRIT-P1 and SPIRIT-P2 trials.
[e] Price submitted to CDR.[1,9]
[f] Régie Assurance Maladie Quebec formulary (Mar 2018).[20]
[g] Alberta Formulary (Mar 2018).[21]

Appendix 2: Summary of Key Outcomes

Results below are specific in comparing ixekizumab to best supportive care using the CDR revised base-case model. Pairwise comparisons to other relevant biologics are not presented.

Table 10: When Considering Only Costs, Outcomes and Quality of Life, How Attractive is Ixekizumab Relative to Best Supportive Care in a Biologic-Naive Population?

Ixekizumab vs. BSC	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	Manufacturer's base case (probabilistic): $65,815 per QALY CDR base case (deterministic): $166,153 per QALY					

BSC = best supportive care; CDR = CADTH Common Drug Review; CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Table 11: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Ixekizumab Relative to Best Supportive Care in a Biologic-Experienced Population?

Ixekizumab vs. BSC	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	Manufacturer's base case (probabilistic): $54,593 per QALY CDR base case (deterministic): $114,520 per QALY					

BSC = best supportive care; CDR = CADTH Common Drug Review; CE = cost-effectiveness; N/A = not applicable; QALY = quality-adjusted life-year; vs. = versus.

Appendix 3: Additional Information

Table 12: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	The model was unable to undertake a probabilistic analysis of multiple comparators.		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

Table 13: Author’s Information

Authors of the Pharmacoeconomic Evaluation Submitted to 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
Author signed a letter indicating agreement with entire document			X
Author had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

No other Health Technology Assessment agencies have reviewed ixekizumab for psoriatic arthritis. It is currently undergoing review by the UK's NICE (National Institute for Health and Care Excellence) (expected publication October 10, 2018).[22] Ixekizumab has been previously reviewed by NICE, INESSS (Quebec's Institut national d'excellence en santé et en services sociaux), the Scottish Medicine Consortium and Australia's PBAC (Pharmaceutical Benefits Advisory Committee) for the indication of plaque psoriasis.[23-26]

Appendix 5: Reviewer Worksheets

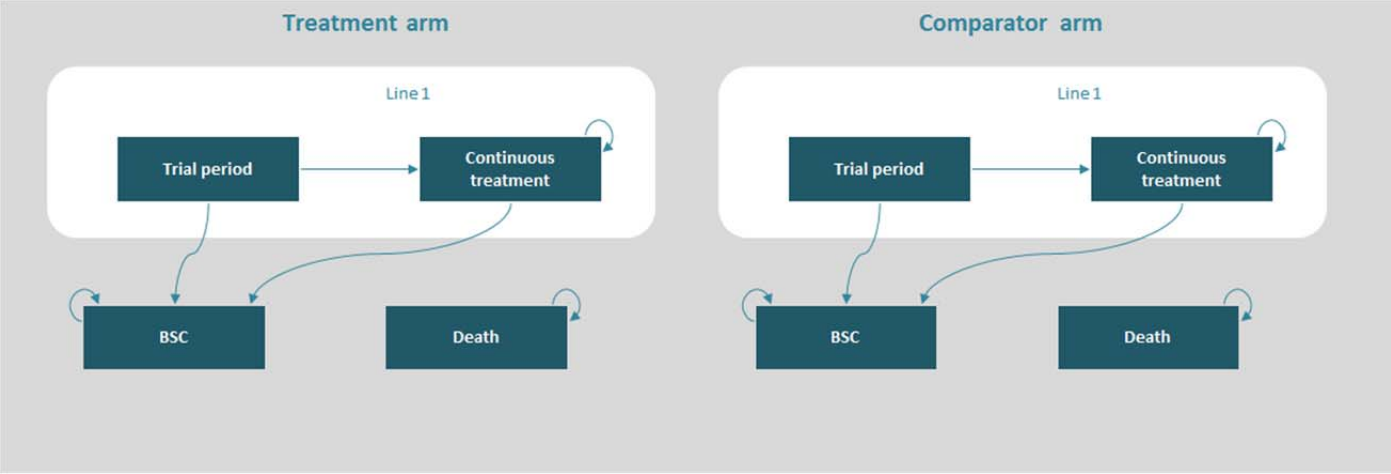
Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis using a Markov model comparing ixekizumab to best supportive care (BSC) and biologics indicated for the treatment of psoriatic arthritis (PsA) (etanercept, biosimlar infliximab, infliximab, apremilast, ustekinumab, adalimumab, golumamb, certolizumab pegol, and secukinumab) among patients with active PsA who have previously failed on a conventional disease-modifying antirheumatic drug (DMARD). BSC was defined as the use of DMARDs (methotrexate, leflunomide, or sulfasalazine).[1] The model population was assumed to have the same characteristics as the average patient in the SPIRIT trials, mean starting age of 51 years, 51.8% male with a mean weight of 87.0 kg.[3,4]

Among patients receiving one of the active interventions, treatment response was assessed after a variable treatment trial period based on Psoriatic Arthritis Response Criteria (PsARC) response (defined as showing improvement in at least two of the following four measures: patient-self assessment, physician assessment, joint pain/tenderness score, and joint swelling score, one of which is the joint pain/tenderness score or joint swelling score, with no worsening in any of these four measures).[1] After the treatment trial period, patients entered either the continued use state or the BSC state. Responders entered and remained in the continued use state until withdrawal due to loss of treatment efficacy or onset of adverse events.[1] Nonresponders and patients who withdrew from the continued treatment state moved to the BSC state. Patients in the BSC state experienced disease progression as reflected by an increment of their Health Assessment Questionnaire–Disability Index (HAQ-DI) score.[1] A constant HAQ-DI score increment of 0.006 per cycle was assigned to BSC nonresponders based on the figure used by Rodgers et al.[6] Incremental cost-utility ratios (ICURs) for all treatments were calculated relative to BSC. Figure 1 shows the model structure for patients receiving active treatment (using apremilast as an example) and for the comparator BSC sequence.

The economic model submitted by the manufacturer also had the flexibility to address treatment sequences in order to investigate the potential cost-effectiveness of ixekizumab at different lines of therapy. The model allowed up to five lines of therapy to be tested.

Figure 1: Schematic of Modelling One Treatment Line



Note: Arrows to death are removed for simplification; however the death state is always reachable irrespective of the current state. The treatment trial period can vary in duration by treatment (as presented in Table 1).
Source: Manufacturer's Pharmacoeconomic Submission.[1]

Table 14: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Manufacturer NMA.[5] Results from a Bayesian fixed-effects analysis were used to derive PsARC response rate. Treatment- and response-specific changes in HAQ-DI and PASI scores were based on the NMA.	Due to poor reporting in the manufacturer-submitted NMA, insufficient evidence was provided to support an assessment of clinical heterogeneity within the included studies. Furthermore, selection of a fixed-effects model with a higher DIC may have been inappropriate for some outcomes. The base case assumed no treatment response for those on BSC. This assumption seems unreasonable. In the SPIRIT trials, the placebo arms were permitted to remain on concomitant conventional DMARD, and the placebo arms reported a 32.1% and 20.3% response on PsARC in SPIRIT-P1 and SPIRIT-P2, respectively, at week 24 of treatment.[3,4] Note that the primary outcome in the ixekizumab clinical trial program was ACR20 while estimates of PsARC were assumed in the model.
Disease Progression: HAQ-DI Score	Assumption from Rogers et al.[6] While patients remained in the continued use state it was assumed that there was no progression in HAQ-DI score, reflecting arrest of disease progression. Nonresponders to active treatment experienced an increase in HAQ-DI score equal to the initial decrement while nonresponders to BSC experienced an initial increase in HAQ-DI score	Unclear whether appropriate or not.

Data Input	Description of Data Source	Comment
	to baseline values with progression at 0.072 per year.	
Baseline Cohort Characteristics	Baseline reflected the average patient in the SPIRIT trials: mean starting age of 51 years, 51.8% male with a mean weight of 87.0 kg.[3,4]	Deemed appropriate by clinical expert consulted in this CDR review.
Utilities-Derivation From PASI and HAQ-DI	Based on the EQ-5D-5L data from the SPIRIT-P1 and SPIRIT-P2 trials,[3,4] mapped to EQ-5D-3L. HAQ-DI and PASI scores from SPIRIT-P1 and SPIRIT-P2 were then regressed on the mapped EQ-5D-3L using an ordinary least regression. The data from SPIRIT-P1 and SPIRIT-P2 were from the active treatment ITT population, meaning only patients who were on ixekizumab or adalimumab. Utilities were based on Canadian preferences sets.[27,28]	It was considered unnecessary to map from EQ-5D-5L to EQ-5D-3L given that the prior is more sensitive and the models were a better fit. The manufacturer's sensitivity analysis demonstrated the impact of this change on the ICUR. It was considered inappropriate to use the active treatment ITT population and exclude placebo patients, particularly since active treatment ITT population models had poorer fit.
Adverse Events	Rates from European Medicines Agency summary of product characteristics, Dixon et al., and Reich et al.[29] Non-melanoma skin cancer Lymphoma Melanoma Severe Infections: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection, urinary tract infection Costs were from the Canadian Institute for Health Information.[30] Disutilities associated with adverse events were not considered.	The manufacturer suggests that adverse events are included in the trial's reported health utilities.[1] However this is unlikely to be the case given that the health utilities in the model are specific to HAQ-DI and PASI score. Furthermore, the trials are unlikely to capture the full effects of adverse events due to their short duration. This may bias the analysis against treatments with fewer adverse events.
Mortality	Canadian age-specific mortality tables, corrected for a PsA standardized mortality ratio of 1.36 as per Ali et al.[7]	Appropriate. Alternative standard mortality ratio applied made little impact on the ICUR in the sensitivity analyses.
Health State–Specific Costs, Derivation From PASI and HAQ-DI	Kobelt et al.[9] Based on UK and Dutch populations.	Although these data were from different countries and more than 15 years old, no more recent data were available.
Drug Costs	Cost of ixekizumab provided by the manufacturer.[1] Cost of relevant comparators from Ontario Drug Benefit formulary[8] or IMS Brogan. Dosages were assumed to be the recommended doses from product monographs. All costs are updated to 2017 Canadian dollars. No additional drug costs were assumed under BSC given that this would be captured in the	Some unit costs for drugs were incorrect; dosing regimens were appropriate. From a review of the Ontario Drug Benefit Formulary,[8] it was found that the cost of apremilast was lower than that reported by the manufacturer (i.e., 18.904 per tablet compared with 19.57). Proportion of baseline conventional DMARD use in the clinical studies informing the NMA is unclear. Specifically, in the SPIRIT trials, current use of conventional DMARD in the placebo arm ranged from

Data Input	Description of Data Source	Comment
	health-state costs derived based on HAQ-DI and PASI score.	65.1% in SPIRIT-P1 to 44.1% in SPIRIT-P2 trials. The manufacturer also excluded the biosimilar price of etanercept, which was reported to be $127.50 for a 25 mg dose and $255.00 for a 50 mg dose.[8] All CDR reanalyses used revised costs for apremilast and the biosimilar price for etanercept.
Administration Costs (Incl. Cost of Monitoring and Follow-Up)	Resource use for monitoring and follow-up were based on clinical expert input and comprised doctor's visits and laboratory testing. Costs for administration were derived from 2015 Schedule of Benefits for Physician Services by the Ministry of Health and Long-Term Care. Costs for physician visits were derived from the 2016 Schedule of Benefits for Physician Services by the Ministry of Health and Long-Term Care. Monitoring costs were taken from the Schedule of Benefits for Physician Services.[31] If necessary, costs were inflated to 2017.	Administration costs are included for treatments that require subcutaneous injection or intravenous infusion. Ixekizumab was assumed to require one tuberculosis Heaf test during the treatment trial period.
Discontinuation	The same annual withdrawal rate was assumed for all biologics to BSC. The input on discontinuation was derived by meta-analysis performed by Rodgers et al. on withdrawal rates (16.5%).[6]	Deemed appropriate by clinical expert.

ACR20 = American College of Rheumatology 20% response; BSC = best supportive care; CDR = CADTH Common Drug Review; DIC = Deviance Information Criterion; DMARD = disease-modifying antirheumatic drug; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HAQ-DI = Health Assessment Questionnaire–Disability Index; ICUR = incremental cost-utility ratio; ITT = intention-to-treat; NMA = network meta-analysis; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; QALY = quality-adjusted life-year.

Table 15: Manufacturer's Key Assumptions

Assumption	Comment
HAQ-DI score rebounds by same amount as initial response, as opposed to rebounding to natural history (i.e., to HAQ-DI score as it would be in the absence of any treatment).	Unclear whether appropriate based on paucity of data. Possibly defensible for some biologics on the basis of radiologic evidence and control of multiple assessed disease areas.[32,33] Addressed as limitation and alternative assumption taken as part of CDR's base case.
No progression of HAQ-DI score during response to treatment.	Unclear whether appropriate based on paucity of data.
Constant per cycle HAQ-DI increase 0.071 upon failure of BSC.	Based on the meta-analysis of Rodgers et al.[6]
Equal withdrawal from treatment for all comparators.	Likely appropriate as per clinical expert.
PsARC definition of response.	PsARC has been commonly used in previous reviews and the clinical data suggest a correlation between ACR20 and PsARC results.
Composition of BSC.	Appropriate, as per clinical expert.
Baseline characteristics of cohort match clinical trial characteristics.	Appropriate, as per clinical expert.
Movement from active treatment to BSC.	Likely inappropriate. First, it is unclear that a DMARD failure population would move to DMARDs. Second, the use of multiple lines of biologics is established practice as per the clinical expert. Addressed by CDR in scenario analysis testing different treatment sequences.

ACR20 = American College of Rheumatology 20% response; BSC = best supportive care; CDR = CADTH Common Drug Review; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire–Disability Index; PsARC = Psoriatic Arthritis Response Criteria.

Manufacturer's Results

The manufacturer's deterministic analyses reported that, in biologic-naive patients, ixekizumab was associated with total costs of $222,859 and 13.79 quality-adjusted life-years (QALYs) over a lifetime (i.e., 48 years). When compared with BSC, ixekizumab was $53,699 more costly with an estimated benefit of 0.816 additional QALYs, leading to an ICUR of $65,815 per QALY gained.[1] Sequential analysis revealed that ixekizumab had higher costs and lower QALYs than secukinumab 150 mg (i.e., ixekizumab was dominated by secukinumab 150 mg). The efficiency frontier comprised BSC, secukinumab 150 mg, and biosimilar infliximab with sequential ICURs of $27,573 per QALY (secukinumab 150 mg) and $99,588 per QALY (biosimilar infliximab). All other comparators were dominated by either secukinumab or biosimilar infliximab.

In the sequential analysis of biologic-experienced patients (Table 5), ixekizumab was associated with total cost of $232,576 and 12.23 QALYs over 48 years. Ixekizumab was $60,475 more costly with an estimated benefit of 1.15 additional QALYs, leading to an ICUR of $52,780 per QALY gained when compared with BSC.[1] Sequential analysis revealed that ixekizumab had higher costs and lower QALYs than secukinumab 150 mg with the efficiency frontier composed of BSC and secukinumab 150 mg. If a payer was not willing to pay more than $21,884 per QALY, BSC would be considered cost-effective; otherwise, at higher willingness-to-pay values, secukinumab 150 mg (sequential ICUR, $21,884 per QALY gained) would be considered cost-effective. All other comparators were dominated by secukinumab 150 mg.

CADTH Common Drug Review Reanalyses

The following scenarios were explored by the CADTH Common Drug Review (CDR) to assess the limitations addressed above. All analyses included revising the price of apremilast and considered biosimilar etanercept to inform the price of the etanercept comparator. Results of most scenario analyses can be found in Table 16.

Regression informing utility calculation: The EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) estimated from the overall intention-to-treat population was used to inform the regression analysis. Although the ICURs increased, there was no change in the overall conclusions in both the biologics-naive (i.e., scenario 1a) and biologics-experienced (i.e., scenario 1b) populations.

HAQ-DI rebound in patients withdrawing from active treatment: HAQ-DI score rebounded to natural progression (i.e., after the biologic treatment was discontinued, the HAQ-DI score increased to the score it would have been had no biologic treatment been used) in patients who withdrew from active treatment and went to BSC. Under this scenario, the expected QALYs associated with biologic treatments decreased and the expected costs increased compared with the manufacturer's base case in both biologics-naive (i.e., scenario 2a) and biologics-experienced (i.e., scenario 2b) populations. This resulted in higher ICURs values for all biologic treatments compared with BSC, and BSC was considered the most likely cost-effective intervention if the decision-maker's cost-effectiveness threshold was under $63,039 per QALY.

Incorporating treatment response while on BSC: Network meta-analysis results from the placebo arm were applied to inform the treatment effectiveness of BSC treatment. The manufacturer's model allowed this change only if the rebound effect back to natural history was also included. This resulted in the expected QALYs for the BSC arm increasing, and the QALYs for the biologic treatment arms decreasing. In this scenario, no biologic treatments were considered cost-effective at $50,000 per QALY.

Ixekizumab as part of a treatment pathway: Exploratory analyses were conducted on the CDR base-case model to address the potential cost-effectiveness of ixekizumab as part of treatment pathway, given that biologic treatments may be used sequentially. The clinical expert recommended that an anti–tumour necrosis factor would be used as first line. In these analyses, biosimilar etanercept was used as first line. Subsequent lines were chosen using the treatment with the lowest ICUR identified from the previous scenario. In all these scenarios, ixekizumab remained dominated (i.e., had higher costs and lower effectiveness) by other treatment options (Table 9).

Table 16: CDR Scenario Analyses for a Biologic-Naive Patient Population (Deterministic Results)

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($/QALY)
	Base Case Submitted by Manufacturer	BSC	13.00	170,815	
		Secukinumab 150 mg	13.87	194,704	27,534
		Apremilast	13.59	199,782	Dominated
		Certolizumab pegol	13.85	214,766	Dominated
		Ixekizumab q.4.w.	13.79	222,859	Dominated
		Adalimumab	13.81	224,210	Dominated
		Secukinumab 300 mg	13.76	225,057	Dominated
		Biosimilar infliximab	14.25	233,275	99,656
		Golimumab	14.05	237,059	Dominated
		Etanercept 50 mg q.w.	14.12	241,494	Dominated
		Etanercept 25 mg 2.q.w.	14.12	242,326	Dominated
1a.	**EQ-5D-5L Measure of Utility**	BSC	14.34	170,815	
		Secukinumab 150 mg	15.13	194,704	30,420
		Apremilast	14.87	198,541	Dominated
		Biosimilar etanercept 50 mg q.w.	15.34	209,657	71,597
		Biosimilar etanercept 25 mg 2.q.w.	15.34	210,515	Dominated
		Certolizumab pegol	15.10	214,766	Dominated
		Ixekizumab q.4.w.	15.06	222,859	Dominated
		Adalimumab	15.07	224,210	Dominated
		Secukinumab 300 mg	15.04	225,057	Dominated
		Biosimilar infliximab	15.48	233,275	166,820
		Golimumab	15.29	237,059	Dominated
2a.	**Rebound to Natural Progression**	BSC	13.00	170,815	
		Secukinumab 150 mg	13.42	197,545	63,039
		Apremilast	13.24	200,746	Dominated
		Biosimilar etanercept 50 mg q.w.	13.58	213,118	96,782
		Biosimilar etanercept 25 mg 2.q.w.	13.58	213,976	Dominated
		Certolizumab pegol	13.42	217,552	Dominated
		Ixekizumab q.4.w.	13.39	225,430	Dominated
		Adalimumab	13.38	226,975	Dominated
		Secukinumab 300 mg	13.37	227,582	Dominated
		Biosimilar infliximab	13.65	237,148	365,620
		Golimumab	13.46	240,817	Dominated
3a.	**Placebo Effect From NMA** (The manufacturer has limited the model so that this scenario can only be run with a rebound effect	BSC	13.22	156,221	
		Secukinumab 150 mg	13.60	185,071	74,783
		Apremilast	13.43	187,791	Dominated
		Biosimilar etanercept 50 mg q.w.	13.76	201,110	105,149
		Biosimilar etanercept 25 mg 2.q.w.	13.76	201,968	Dominated

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($/QALY)
	back to natural progression.)	Certolizumab pegol	13.60	205,052	Dominated
		Ixekizumab q.4.w.	13.58	212,754	Dominated
		Adalimumab	13.56	214,459	Dominated
		Secukinumab 300 mg	13.56	214,871	Dominated
		Biosimilar infliximab	13.85	223,012	231,445
		Golimumab	13.67	226,595	Dominated
4a.	**CDR Base-Case Reanalysis**	BSC	14.57	156,221	
		Secukinumab 150 mg	14.93	185,071	79,331
		Apremilast	14.77	187,791	Dominated
		Biosimilar etanercept 50 mg q.w.	15.05	201,110	137,261
		Biosimilar etanercept 25 mg 2.q.w.	15.05	201,968	Dominated
		Certolizumab pegol	14.91	205,052	Dominated
		Ixekizumab q.4.w.	14.91	212,754	Dominated
		Adalimumab	14.88	214,459	Dominated
		Secukinumab 300 mg	14.89	214,871	Dominated
		Biosimilar infliximab	15.16	223,012	304,342
		Golimumab	14.99	226,595	Dominated

2.q.w. = twice weekly; BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; q.4.w. = every 4 weeks; q.w. = once weekly.

Table 17: CDR Scenario Analyses for Biologic-Experienced Patient Population (Deterministic Results)

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($/QALY)
	Base Case, Submitted by Manufacturer	BSC	11.09	172,102	
		Secukinumab 150 mg	12.27	197,987	21,884
		Certolizumab pegol	12.23	220,360	Dominated
		Secukinumab 300 mg	12.15	231,779	Dominated
		Ixekizumab q.4.w.	12.23	232,576	Dominated
1b.	**EQ-5D-5L Measure of Utility**	BSC	14.00	172,102	
		Secukinumab 150 mg	14.87	197,987	28,682
		Certolizumab pegol	14.84	220,360	Dominated
		Secukinumab 300 mg	14.78	231,779	Dominated
		Ixekizumab q.4.w.	14.84	232,576	Dominated
2b.	**Rebound to Natural Progression**	BSC	11.09	172,102	
		Secukinumab 150 mg	11.76	200,989	42,718
		Certolizumab pegol	11.73	223,303	Dominated
		Secukinumab 300 mg	11.70	234,484	Dominated
		Ixekizumab q.4.w.	11.73	235,474	Dominated
3b.	**Placebo Effect From NMA** (The manufacturer has limited the model so that this scenario can only be run with a rebound effect back to natural progression.)	BSC	11.54	154,560	
		Secukinumab 150 mg	12.13	186,248	52,885
		Certolizumab pegol	12.11	208,523	Dominated
		Secukinumab 300 mg	12.07	219,469	Dominated
		Ixekizumab q.4.w.	12.11	220,639	Dominated
4b.	**CDR Base-Case Reanalysis**	BSC	14.30	154,560	
		Secukinumab 150 mg	14.72	186,248	74,949
		Certolizumab pegol	14.70	208,523	Dominated
		Secukinumab 300 mg	14.68	219,469	Dominated
		Ixekizumab q.4.w.	14.71	220,69	Dominated

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; q.4.w. = every 4 weeks.

Table 18: CDR Base-Case Reanalysis Testing Sequence Pathways

	Scenario	Treatments	QALYs	Cost ($)	ICUR ($/QALY)
4.1	**Used as Second-Line Treatment** Treatment sequence: biosimilar etanercept 50 mg q.w. → *treatment comparison*	BSC	15.05	201,110	
		Secukinumab 150 mg	15.48	226,363	28,370
		Apremilast	15.31	228,933	Dominated
		Certolizumab pegol	15.46	244,252	Dominated
		Ixekizumab	15.44	251,327	Dominated
		Adalimumab	15.43	252,727	Dominated
		Secukinumab 300 mg	15.42	253,318	Dominated
		Biosimilar infliximab	15.69	262,369	102,405
		Golimumab	15.53	265,542	Dominated
4.2	**Used as Third-Line Treatment** Treatment sequence: biosimilar etanercept 50 mg q.w. → secukinumab 150 mg → *treatment comparison*	BSC	15.48	226,363	
		Apremilast	15.76	251,141	Extendedly dominated
		Certolizumab pegol	15.91	264,850	Extendedly dominated
		Ixekizumab	15.90	271,354	Dominated
		Adalimumab	15.89	272,523	Dominated
		Biosimilar infliximab	16.15	281,107	81,557
		Golimumab	16.00	283,923	Dominated
4.3	**Used as Fourth-Line Treatment** Treatment sequence: biosimilar etanercept 50 mg q.w. → secukinumab 150 mg → biosimilar infliximab → *treatment comparison*	BSC	16.15	281,107	
		Apremilast	16.45	301,836	68,884
		Certolizumab pegol	16.59	313,366	79,615
		Ixekizumab q.4.w.	16.57	319,048	Dominated
		Adalimumab	16.57	319,923	Dominated
		Golimumab	16.69	329,442	9,317
4.4	**Used as Fifth-Line Treatment** Treatment sequence: biosimilar etanercept 50 mg q.w. → secukinumab 150 mg → biosimilar infliximab → apremilast → *treatment comparison*	BSC	16.45	301,836	
		Certolizumab pegol	16.88	330,670	66,910
		Ixekizumab q.4.w.	16.86	335,862	Dominated
		Adalimumab	16.86	336,587	Dominated
		Golimumab	16.98	345,078	145,881

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; q.4.w. = every 4 weeks.

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