CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

IXEKIZUMAB (Taltz)

(Eli Lilly Canada Inc.)

Indication: For the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy.

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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

AE	adverse event
AS	ankylosing spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
bDMARD	biologic disease-modifying antirheumatic drug
cDMARD	conventional disease-modifying antirheumatic drug
CDR	CADTH Common Drug Review
CT	conventional therapy
CUA	cost-utility analysis
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
IXE	ixekizumab
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
NSAID	nonsteroidal anti-inflammatory drug
QALY	quality-adjusted life-year
TNFi	tumour necrosis factor inhibitor
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Ixekizumab (Taltz)
Study question	What is the incremental cost-effectiveness of ixekizumab compared to relevant treatment options in patients with AS over a lifetime horizon from the perspective of a public payer?
Type of economic evaluation	CUA
Target population	Adults with active AS who have responded inadequately to, or are intolerant to CT
Treatment	Ixekizumab solution for injection
Outcome	QALYs
Comparators	• Biologic naive: CT (e.g., corticosteroids, nonsteroidal anti-inflammatory drugs, or cDMARDs such as sulfasalazine, methotrexate, and leflunomide) adalimumab, etanercept, biosimilar etanercept, and secukinumab • TNFi-experienced: CT
Perspective	Canadian publicly funded health care payer
Time horizon	Lifetime (until 100 years of age)
Results for base case	• Biologic naive: In a sequential analysis, ixekizumab dominated etanercept, and extendedly dominated biosimilar etanercept and adalimumab. The ICER for ixekizumab compared to secukinumab was $536,001 per QALY gained. • TNFi-experienced: The ICER for ixekizumab compared to CT was $52,122 per QALY gained.
Key limitations	• The sponsor did not consider all relevant comparators. According to the clinical expert consulted by CADTH, all bDMARDs are relevant comparators in both the biologic-naive and TNFi-experienced populations. In the biologic-naive population, certolizumab pegol, golimumab, and infliximab were not considered. In the TNFi-experienced population, certolizumab pegol, golimumab, infliximab, and the other bDMARDs considered in the biologic-naive population were missing; the exclusion of secukinumab was particularly notable. • All patients who discontinued a biologic treatment were inappropriately assumed to switch to lifelong CT. According to the clinical expert consulted by CADTH, this does not reflect clinical practice. • The comparative effectiveness of ixekizumab is uncertain. CADTH clinical reviewers were uncertain about the credibility of the sponsor's ITC due to insufficient information regarding the methodology and the quality of included studies. The BASDAI 50 results from the COAST-W trial used in the TNFi-experienced analysis were also uncertain as the end point was not controlled for multiplicity. Additionally, the durability of the estimated comparative effectiveness beyond the observed 12- to 16-week period in the ITC is uncertain. The ITC also did not reflect expected clinical practice in Canada. The ITC results incorporated into the biologic-naive model were based on patients who received both 80 mg and 160 mg ixekizumab as initial doses, while the expected initial dose in the biologic-naive population is 80 mg. The BASDAI 50 response criteria used in the ITC (and in the submitted CUAs) also does not fully reflect the varied Canadian reimbursement practice which may also consider other endpoints including BASFI, HAQ, return to work, or a minimum two-point reduction in the pain component of BASDAI. This adds further uncertainty to the generalizability of the CUA results.

	• The modelling of disease-specific mortality and disease progression was based on international data that partly included a period before multiple biologic treatments were available. Additionally, although BASFI increases from radiographic disease progression were based on a study that observed increases in the mSASSS, the model inappropriately allowed BASFI to increase beyond the possible range of mSASSS values. • The algorithm used to map BASDAI and BASFI scores to health utility values had poor validity. In the TNFi-experienced population analysis, the algorithm inappropriately estimated a positive correlation between BASDAI and health utility values in contrast to the clinical expectation of a negative correlation. The algorithm also allowed for utility estimates that were higher than 0.885, which is the highest reported mean EQ-5D-3L health state utility value in the general Canadian population and allowed estimates higher than one (beyond the conceptual maximum utility value) in the TNFi-experienced population. • The sponsor's algorithm to map non-biologic treatment-related disease management costs to BASFI scores was also uncertain as it was based on outdated international cost data and its generalizability to the current Canadian context is unclear.

CDR estimates	• The CADTH reanalysis for both the biologic-naive population and the TNFi-experienced population incorporated the EQ-5D-5L utility algorithm from the biologic-naive population analysis to appropriately incorporate the negative correlation between BASDAI and health utility values. The reanalysis for the biologic-naive population further incorporated comparative efficacy results for the 80 mg ixekizumab initial dose subgroup from the sponsor's ITC and also included Erelzi, an etanercept biosimilar, as a comparator. CADTH base-case ICERs for ixekizumab were:
	  ○ $973,100 per QALY gained compared to adalimumab in the biologic-naive population
	  ○ $70,448 per QALY gained compared to CT in the TNFi-experienced population
	  ○ Price reductions of more than 44% in the biologic-naive population, and more than 16% in the TNFi-experienced population are required for ixekizumab to be considered an optimal treatment at a willingness-to-pay threshold of $50,000 per QALY.
	• CADTH could not address many of the limitations, including the uncertain comparative effectiveness of ixekizumab compared with relevant comparators, some of which have been excluded from the analyses, and the uncertain generalizability of the modelled natural history, health utility algorithm, and disease management costs. The cost-effectiveness of ixekizumab is highly dependent on comparative effectiveness estimates, and this remains an area of uncertainty (e.g., relevant comparators such as certolizumab pegol, golimumab, and infliximab were not considered).

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug; CT = conventional therapy; CUA = cost-utility analysis; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HAQ = health assessment questionnaire; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; QALY = quality-adjusted life-year; TNFi = tumour necrosis factor inhibitor.

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Drug	Ixekizumab (Taltz)
Indication	Treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or are intolerant to conventional therapy
Reimbursement request	As per indication
Dosage form	Solution for subcutaneous injection 80 mg/1.0 mL
NOC date	February 4, 2020
Sponsor	Eli Lilly Canada Inc.

Executive Summary

Background

Ixekizumab (IXE) (Taltz) is a biologic disease-modifying antirheumatic drug (bDMARD) indicated for use in adult patients with active ankylosing spondylitis (AS) who have responded inadequately to, or are intolerant to conventional therapy (CT).[1] CT may involve corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and conventional disease-modifying antirheumatic drugs (cDMARDs) such as sulfasalazine, methotrexate, and leflunomide[1], although according to the latest clinical guideline,[2] corticosteroids should not be used as a long-term treatment for AS, and cDMARDs have not shown efficacy in managing AS and are not recommended to be concurrently administered with biologic treatments.

The dosage form of IXE is an 80 mg/mL solution in a pre-filled syringe or pen, intended for patients to self-administer subcutaneously. The recommended dose for adult AS patients is an 80 mg injection given every four weeks. Limited data also suggests that some tumour necrosis factor inhibitor (TNFi)-experienced patients with AS may benefit from a 160 mg starting dose.[1] At the sponsor's submitted price of $1,582.24 per 80 mg dose,[3] the annual cost of IXE is $20,569 in patients with AS, while in patients who started with a 160 mg initial dose, the first-year cost of IXE is $22,151 per patient, followed by $20,569 per patient in subsequent years.

IXE was previously reviewed by CADTH in 2016 for the indication of moderate to severe plaque psoriasis,[4] and in 2018 for active psoriatic arthritis in patients with inadequate response to cDMARDs.[5] CADTH Canadian Drug Expert Committee (CDEC) recommended listing IXE for both indications. For moderate to severe plaque psoriasis, CDEC recommended listing with the clinical criteria limiting its use to patients with a documented inadequate response, contraindication, or intolerance to conventional systemic therapies such as methotrexate and cyclosporine, and recommending that treatment should be discontinued if response to treatment with IXE has not been demonstrated after 12 weeks.[4] For active psoriatic arthritis in patients with inadequate response to cDMARDs, CDEC recommended listing with the condition that IXE should provide cost savings for drug plans relative to other biologic treatments reimbursed for the treatment of psoriatic arthritis.[5] The sponsor's submitted price for IXE was $1,519 per 80 mg dose at the time of the 2016 CADTH Common Drug Review (CDR) submission,[4] and $1,544.82 per 80 mg dose at the time of the 2018 CDR submission.[5]

The sponsor submitted cost-utility analyses (CUAs) for patients with active AS who have inadequate response or intolerance to CT, for both the biologic-naive and the TNFi-experienced populations separately.[6] In the biologic-naive population, IXE was compared to CT and a limited set of bDMARDs (i.e., adalimumab, etanercept, etanercept biosimilar [Brenzys], and secukinumab). In the TNFi-experienced population, IXE was compared to CT only. In both analyses, half of the patients receiving IXE were assumed to receive an initial dose of 80 mg, and the other half of the patients were assumed to receive the higher 160 mg initial dose described in the product monograph. The analyses used a lifetime time horizon (until patients had died or reached 100 years of age) and were conducted from the perspective of a publicly funded health care payer with costs and quality-adjusted life-years (QALYs) discounted at 1.5% per year.

The modelled biologic-naive and TNFi-experienced populations matched the baseline characteristics of the average patient in the sponsor's COAST-V[7] and COAST-W[8] trials respectively. Patients who received a biologic treatment began the model in a short-term variable biologic treatment trial period (ranging from 12 weeks for adalimumab, etanercept, and biosimilar etanercept, to 16 weeks for IXE and secukinumab) to assess Bath AS disease activity index (BASDAI) 50 response. Patients who responded moved to a long-term maintenance state, and those who did not respond would move to a CT state. Patients who discontinued treatment (11% annual biologic treatment discontinuation rate was assumed) during the long-term maintenance period would also move to the CT state. The long-term maintenance and CT health states were modelled as four-week cycles. Patients could also enter a death state from any other health state. Treatment-dependent probabilities of BASDAI 50 response were informed by the sponsor's indirect treatment comparison (ITC)[9] for the biologic-naive population and the COAST-W trial[8] for the TNFi-experienced population. Patients who received CT stayed on CT regardless of response until end of time horizon or death.

BASDAI and Bath AS function index (BASFI) scores for patients were modelled across the health states over the model time horizon and were converted to EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) health utility values. Upon treatment response, responders received treatment-dependent BASDAI and BASFI score reductions based on either the sponsor's ITC[9] (for the biologic-naive population) or the COAST-W trial[8] (for the TNFi-experienced population), and remained on maintenance treatment. After the initial treatment response assessment period, patients were assumed to experience disease progression depending on whether they continued receiving a biologic treatment (0.034 BASFI units per year) or CT (0.082 BASFI units per year). Upon treatment discontinuation, the BASDAI score in former responders was assumed to revert to their baseline BASDAI value (i.e., before treatment), and the BASFI score was assumed to increase by the amount of initial BASFI score reduction due to treatment response. Mortality was modelled based on the general Canadian life table[10] and the additional mortality risk associated with AS.[11] BASFI scores were also used to derive non-biologic treatment-associated disease management costs. Other costs (biologic drug acquisition, administration, and adverse event) were derived from Canadian sources.[12-14]

The sponsor reported that in the biologic-naive population, only CT, secukinumab, and IXE were found to be on the cost-effectiveness efficiency frontier; IXE dominated etanercept and extendedly dominated adalimumab and biosimilar etanercept. IXE was associated with an incremental cost-effectiveness ratio (ICER) of $536,001 per QALY compared to secukinumab. At a willingness-to-pay (WTP) threshold of $50,000 per QALY, IXE had 0.2% probability of being the optimal treatment in the biologic-naive population. In the TNFi-

experienced population, IXE was associated with an ICER of $52,122 per QALY gained compared with CT. At a WTP threshold of $50,000 per QALY, IXE had a 50% probability of being the optimal treatment in the TNFi-experienced population.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the model submitted by the sponsor.

The pharmacoeconomic model did not consider all relevant comparators. According to the clinical expert consulted by CADTH, all indicated bDMARDs that were not considered in the submitted analysis for biologic-naive populations (i.e., certolizumab pegol, golimumab, and infliximab), and relevant bDMARDs for TNFi-experienced populations (i.e., all TNFis with an AS indication and secukinumab) may be tried in different sequences of biologics following initial treatment failure. The cost-effectiveness of IXE for this indication may be unknown as the inclusion of these other comparators may affect whether IXE would remain on the cost-effectiveness efficiency frontier. Additionally, the modelled patients were inappropriately assumed to discontinue biologic treatment and switch to lifelong CT. This does not reflect clinical practice, and the impact of different biologic treatment sequences on the cost-effectiveness of IXE should have been explored.

Furthermore, the limitations associated with the sponsor's indirect treatment comparison (ITC) and the COAST-W trial contributed to uncertainty in the modelled comparative effectiveness of IXE compared to other biologics and CT. CADTH clinical reviewers were uncertain about the credibility of the ITC due to insufficient information regarding the methodology and the quality of included studies. The BASDAI 50 results from the COAST-W trial used in the TNFi-experienced population analysis were also uncertain as the end point was not controlled for multiplicity. It is also unclear whether the estimated comparative effectiveness from these sources would be durable over the long term as the ITC and the COAST-W trial findings only reflect trial results of more than 12 to 16 weeks of treatment. Model inputs sourced from the ITC data also did not reflect the expected clinical pathway in Canada. The ITC results for the biologic-naive population incorporated both 80 mg and 160 mg initial doses of IXE, while the expected initial dose in this population is 80 mg. The ITC (and the submitted CUAs) used the BASDAI 50 response criteria which does not fully reflect the varied Canadian biologic reimbursement criteria which may also consider other endpoints including BASFI, health assessment questionnaire, return to work, or a minimum two-point reduction in the pain component of BASDAI. This adds further uncertainty to the generalizability of the pharmacoeconomic model results.

The source data underlying the modelling of disease-specific mortality and disease progression were based on international data that partly included a period that reflects an outdated treatment environment before multiple biologic treatments were available. According to the clinical expert consulted by CADTH, the inclusion of the period before the availability of bDMARDs may introduce an upward bias in disease progression and mortality (i.e., faster disease progression and increased mortality). The inclusion of the period after the availability of bDMARDs may introduce a downward bias in terms of disease progression (i.e., slower disease progression) as the sponsor included data from this period to model the baseline disease progression in patients who only receive CT. Furthermore, although the modified Stoke AS spinal score (mSASSS) was used to derive the rate of disease progression in terms of BASFI increase over the time horizon, the modelled BASFI increase due to radiographic disease progression exceeded the range that is possible on the mSASSS. Collectively, these limitations render the modelled natural history to be uncertain.

The sponsor used algorithms to map BASDAI and BASFI scores to health utility values that had poor construct validity. The algorithms allowed for utility estimates that were higher than 0.885 in both the biologic-naive and TNFi-experienced populations (the highest reported mean EQ-5D-3L health state utility value for Canadians in the general population) and one in the TNFi-experienced population (the conceptual maximum utility value). The algorithm for the TNFi-experienced population also did not reflect the clinical expectation that BASDAI would be negatively correlated with health utility values. The sponsor's algorithm to map BASFI scores to disease management costs (non-biologic and treatment-related) was also uncertain. The algorithm was based on outdated international cost data from 1996 and 1997 and its generalizability to the current Canadian disease management context is unclear.

The CADTH reanalysis for both the biologic-naive population and the TNFi-experienced population incorporated the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) utility algorithm from the biologic-naive population analysis to appropriately incorporate the negative correlation between BASDAI and health utility values. The reanalysis for the biologic-naive population further incorporated comparative efficacy results for the 80 mg IXE initial dose subgroup from the sponsor's ITC, and included Erelzi, an etanercept biosimilar, as a comparator.

Conclusions

In biologic-naive adults with active AS who have inadequate response or intolerance to CT, CADTH estimated that IXE would be associated with an ICER of $973,100 per QALY gained compared to adalimumab. In the TNFi-experienced population, IXE was associated with an ICER of $70,448 per QALY gained compared to CT. Based on CADTH reanalyses, price reductions of more than 44% and more than 16% would be required for IXE to be the optimal intervention at a WTP threshold of $50,000 per QALY gained in biologic-naive patients and TNFi-experienced patients, respectively.

However, considerable uncertainty remains in this analysis given the identified limitations that could not be addressed, including uncertain comparative effectiveness (exclusion of relevant comparators and issues with the sponsor's ITC) and uncertain generalizability of the modelled natural history, health utility algorithm, and disease management costs. Of note, the cost-effectiveness of IXE is likely to be affected by its relationship to other relevant comparators, and this relationship remains unknown as the analyses excluded relevant comparators such as certolizumab pegol, golimumab, and infliximab. CADTH notes that while the annual cost of IXE ranges between $20,569 to $22,151, the annual cost of the other interleukin inhibitor biologic, secukinumab, ranges between $9,973 to $13,298 (Appendix 1).

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted CUAs for patients with AS who have inadequate response or intolerance to CT for the biologic-naive and TNFi-experienced populations separately.[6] In the biologic-naive population, IXE was compared to CT and a limited set of bDMARDs. The bDMARD comparators considered in the model included adalimumab, etanercept, etanercept biosimilar Brenzys, and secukinumab, but not certolizumab pegol, golimumab, or infliximab which are also indicated for AS. Half of the patients receiving IXE were assumed to receive an initial dose of 80 mg, and the other half of the patients were assumed to receive the higher 160 mg initial dose. This assumption reflected the assignment of initial doses in the COAST-V and COAST-W trials[7,8]. In the TNFi-experienced population, IXE was compared to CT only. The analyses used a lifetime time horizon (until patients had died or reached 100 years of age) and were conducted from the perspective of a publicly funded health care payer with costs and QALYs discounted at 1.5% per year.

The modelled biologic-naive and TNFi-experienced populations matched the baseline characteristics of the average patient in the sponsor's COAST-V and COAST-W trials respectively.[7,8] The population for the biologic-naive model was 81.0% male with a mean weight of 78.0 kg and had a mean starting age of 42 years while the population for the TNFi-experienced model was 80.1% male with a mean weight of 83.2 kg and had a mean starting age of 46 years. Patients who received a biologic treatment began the model in a short-term variable biologic treatment trial period (ranging from 12 weeks for adalimumab, etanercept, and biosimilar etanercept, to 16 weeks for IXE and secukinumab) to assess BASDAI 50 response (Figure 1). Patients that responded would move to a long-term maintenance state and those that did not respond would move to a CT state. Patients that discontinued treatment (11% annual biologic treatment discontinuation rate assumed) during the long-term maintenance period would also move to the CT state. The long-term maintenance and CT health states were modelled as four-week cycles. Patients could also enter a death state from any other health state. Treatment-dependent probabilities of BASDAI 50 response were informed by sponsor's ITC for the biologic-naive population, and the COAST-W trial for the TNFi-experienced population. Patients who received CT stayed on CT regardless of response until end of time horizon or death.

BASDAI and BASFI scores of patients were modelled across the health states over the time horizon and were converted to EQ-5D-3L health utility values using a mapping algorithm derived using the COAST-V trial[7] for the biologic-naive population and the COAST-W trial[8] for the TNFi-experienced population. Upon treatment response, responders received treatment-dependent BASDAI and BASFI score reductions based on either the sponsor's ITC[9] (for the biologic-naive population) or the COAST-W trial[8] (for the TNFi-experienced population), and remained on maintenance treatment. After the initial treatment response assessment period, patients were assumed to experience disease progression at a constant increment of 0.034 BASFI units per year while on biologic treatment and 0.082 BASFI units per year while on CT as per a UK AS economic model.[15] Upon treatment discontinuation, the BASDAI score in former responders was assumed to revert to their baseline BASDAI value, and the BASFI score was assumed to increase by the amount of the initial BASFI score reduction due to treatment response in addition to the BASFI increase due to disease progression. Mortality transitions were based on the Canadian general life table[10] and

corrected for the sex-specific mortality risk associated with AS based on a 2011 analysis of a cohort of Norwegian patients.[11]

Adverse events (AEs) were not assumed to affect health utility values but were costed as a weighted average of various types of infection as informed by Ontario Case Costing Initiative costs.[12] Treatment-dependent infection rates were based on the summary of product characteristics reported by the European Medicines Agency. Drug acquisition costs for biologic treatments and resource unit costs were from Ontario provincial sources,[13,14] while biologic treatment-related resource utilization was assumed to be equivalent across biologic treatments and was informed by clinical expert feedback collected by the sponsor. The model did not directly include drug costs for CT. Instead, the sponsor adapted the cost algorithm from the 2016 UK AS economic model[15] to map BASFI score to non-biologic treatment-related disease management costs (i.e., excludes biologic drug acquisition, administration, monitoring, and AE costs) in 2018 Canadian dollars.

Sponsor's Base Case

The sponsor's probabilistic base-case results (based on 2,000 iterations) are presented in Table 2 (biologic-naive population) and Table 3 (TNFi-experienced population). In the biologic-naive population, only CT, secukinumab, and IXE were found to be on the cost-effectiveness efficiency frontier; IXE dominated etanercept and extendedly dominated adalimumab and biosimilar etanercept. Compared to secukinumab, IXE was associated with 0.03 additional QALYs at an additional cost of $8,377, resulting in an ICER of $536,001 per QALY gained. At a WTP threshold of $50,000 per QALY, IXE had a 0.2% probability of being the optimal treatment in the biologic-naive population. In the TNFi-experienced population, IXE was associated with 0.44 additional QALYs at an additional cost of $23,068 compared to CT, resulting in an ICER of $52,122 per QALY gained. At a WTP threshold of $50,000 per QALY, IXE had a 50% probability of being the optimal treatment in the TNFi-experienced population.

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

Drug	Total costs ($)	Total QALYs	Incremental cost ($)	Incremental QALYs	Incremental cost per QALY ($)
CT	366,993	18.48	—	—	Reference
Secukinumab	379,679	18.94	12,686	0.46	27,368
Etanercept biosimilar	391,026	18.96	11,347	0.02	Extendedly dominated
Adalimumab	410,495	18.99	19,468	0.03	Extendedly dominated
Ixekizumab	***418,871***	***19.01***	***8,377***	***0.03***	***536,001***
Etanercept	420,177	18.96	1,306	–0.05	Dominated

CT = conventional therapy; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[6]

Table 3: Summary of Sequential Analysis Results of the Sponsor's Base Case for TNF Inhibitor-Experienced Patients

Drug	Total costs ($)	Total QALYs	Incremental cost ($)	Incremental QALYs	Incremental cost per QALY ($)
CT	418,453	13.61	—	—	Reference
Ixekizumab	***441,521***	***14.05***	***23,068***	***0.44***	***52,122***

CT = conventional therapy; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[6]

Summary of the Sponsor's Sensitivity Analyses

The sponsor explored a number of parametric and structural uncertainties through additional sensitivity analyses (i.e., time horizon, discount rate, initial dose subgroup, and alternative utility algorithms). Of note, the biologic-naive and the TNFi-experienced models were found to be sensitive to the following: time horizon; discount rates; use of the IXE 80 mg initial dose subgroup data from the sponsor's ITC for BASDAI 50 response rate, BASDAI, and BASFI reductions; and alternative utility algorithms (sponsor's alternative utility algorithm based on EQ-5D-5L and algorithms sourced from other studies[16-18]). The sponsor's sensitivity analyses with regards to the 80 mg initial dose subgroup and utility equations are described as follows:

- **IXE 80 mg initial dose subgroup**: In order to model the subgroup of patients who would be expected to only receive the 80 mg initial dose of IXE, the sponsor excluded patients who received the 160 mg initial dose from the model and applied the BASDAI 50 response rates, BASDAI reduction, and BASFI reduction based on an ITC sensitivity analysis that incorporated only a subgroup of patients who received the 80 mg initial dose. For the biologic-naive population, the use of this subgroup data would be more consistent with the recommended initial dose in the Canadian product monograph for IXE. The sensitivity analysis of the biologic-naive population pharmacoeconomic model found that the list of comparators that comprise the cost-effectiveness efficiency frontier expanded to include adalimumab for the biologic-naive population. Total QALYs for patients treated with IXE also decreased from 19.02 QALYs to 18.99 QALYs. Consequently, the ICER of IXE increased to $1,229,765 per QALY gained for the biologic-naive population (Table 13). The 80 mg initial dose subgroup analysis in the TNFi-experienced population did not produce cost-effectiveness results that were substantially different from the base case.
- **Utility Equations**: The sponsor explored a range of utility equations that transform BASDAI and BASFI scores to health utility values as alternatives to the sponsor's base-case EQ-5D-3L utility equations based on COAST-V trial data for biologic-naive patients and COAST-W trial data for TNFi-experienced patients. The equations from the Wailoo et al. (2015) study,[18] the McLeod et al. (2007) study,[16] the 2016 National Institute for Health and Care Excellence (NICE) secukinumab submission,[17] and the sponsor's utility equation based on EQ-5D-5L were explored. Amongst these, the equations from the Wailoo et al. (2015) study[18] and the 2016 NICE secukinumab submission[17] had the largest impact on the cost-effectiveness results for the biologic-naive population. Compared to the base-case analysis (which estimated the ICER of IXE to be $536,001 per QALY gained), these equations reduced the ICER of IXE by approximately half ($232,721 per QALY gained with the 2016 NICE secukinumab submission equation[17] and $263,311 per QALY gained

with the Wailoo et al. equation[18]). For the TNFi-experienced population, most of the alternative utility equations reduced the ICER of IXE (ranging from $30,932 per QALY gained to $38,825 per QALY gained) from $52,122 per QALY gained in the base-case analysis, except for the equation from the Wailoo et al. (2015) study,[18] which increased the ICER of IXE to $85,524 per QALY gained.

Limitations of the Sponsor's Submission

The following limitations were identified with the sponsor's pharmacoeconomic submission:

- **Model did not consider all relevant comparators**: The sponsor's ITC was unable to consider the relative efficacy of other relevant comparators including certolizumab pegol, golimumab, and infliximab. These comparators are relevant for the biologic-naive population, and the cost-effectiveness of IXE compared to these other comparators remains unknown. The inclusion of these comparators may affect whether IXE would remain on the cost-effectiveness efficiency frontier for the biologic-naive population.

  In the analysis for the TNFi-experienced population, the sponsor only compared IXE to CT. According to the clinical expert consulted by CADTH, other bDMARDs remain relevant comparators in the TNFi-experienced population as different biologics may be tried following previous biologic failure. Considering that efficacy data were informed by a TNFi-experienced population, the inclusion of secukinumab, an interleukin-17 inhibitor, would have been especially relevant. The cost-effectiveness of IXE compared to the other comparators also remains unknown for the TNFi-experienced population.
- **Inappropriate treatment discontinuation assumption**: The sponsor assumed in the analyses for both the biologic-naive and the TNFi-experienced population that patients would switch to CT upon failure of the first modelled biologic therapy. This does not match the recommendations of a clinical guideline[2] and of the clinical expert consulted by CADTH, that suggest that the exploration of other biologic treatment options before lifetime CT treatment would be considered. CADTH explored a range of treatment sequence scenarios in scenario analyses to address this limitation.
- **Uncertain comparative effectiveness of IXE compared to CT and biologics**: According to the CADTH clinical reviewers, there was insufficient information regarding the ITC methodology and the quality of the included studies, limiting the ability to assess the clinical heterogeneity of the studies and rendering the credibility of the findings uncertain. The BASDAI 50 results from the COAST-W trial used in the TNFi-experienced population analysis were also uncertain as the end point was not controlled for multiplicity. Furthermore, as the ITC and the COAST-W trial only reflect trial results up to 12 to 16 weeks of treatment, it is uncertain whether the comparative efficacy estimated by these sources would be durable over a longer term. Additionally, the sponsor's base case for the biologic-naive population included efficacy data of patients from the COAST-V trial, which included both patients who received an 80 mg initial dose of IXE and patients who received a 160 mg initial dose. According to the clinical expert consulted by CADTH, the biologic-naive population in Canada would be expected to receive an 80 mg initial dose, consistent with the recommendation in the product monograph.[1] Lastly, exclusively incorporating the BASDAI 50 response criteria into the model does not fully reflect clinical practice, as the reimbursement criteria for biologic drugs for AS vary across Canada and may also consider other endpoints including BASFI, health assessment questionnaire, return to work, or a minimum two-point reduction in the pain component of BASDAI. It is uncertain how efficacy based on different response criteria would impact the cost-effectiveness results.

- **Uncertain mapping of BASDAI and BASFI scores to health utility values:** The sponsor used a regression analysis of BASDAI, BASFI, and EQ-5D-5L data from the COAST-V trial (for the biologic-naive population) and COAST-W trial (for the TNFi-experienced population) to inform the EQ-5D-3L-based health utility values in the submitted CUAs. A number of limitations associated with these utility algorithms contribute to the uncertainty associated with the QALYs captured by the CUAs. Firstly, the modelled relationship between BASDAI and health utility values modelled in the TNFi-experienced population analysis did not match clinical expectations. Although the increase in BASDAI score reflects increased disease activity, the utility algorithm associated increased BASDAI scores with increased health utility values. This relationship was appropriately maintained as a negative correlation in the biologic-naive population model. Secondly, the utility values were allowed to be higher than 0.885 (the highest reported mean EQ-5D-3L health state utility value in the general Canadian population[19]) in the biologic-naive population model, and higher than one (the maximum conceptual utility value equivalent to perfect health) in the TNFi-experienced population model.

  Furthermore, during the process of deriving the utility algorithm for the submitted model, the sponsor transformed the EQ-5D-5L score from the COAST-V and COAST-W trials to EQ-5D-3L. 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 three to five.[20] It is unclear what the sponsor's rationale was for transforming the EQ-5D-5L scores to an older and less sensitive EQ-5D-3L version.

- **Uncertain generalizability of the modelled natural history of the disease :** The sponsor modelled the mortality associated with AS based on a cohort of Norwegian patients that were followed since 1977.[11] Similarly, the sponsor modelled BASFI increase due to radiographic progression based on mSASSS measured from a cohort of Dutch, Belgian, and French patients that began in 1996.[21] The generalizability of these data to the Canadian population is uncertain especially considering that the data are partly from a period before the availability of multiple biologic treatments. According to the clinical expert consulted by CADTH, the inclusion of the period before the availability of bDMARDs may introduce an upward bias in disease progression and mortality (i.e., faster disease progression and increased mortality). The inclusion of the period after the availability of bDMARDs may introduce a downward bias in terms of disease progression (i.e., slower disease progression) as the sponsor included data from this period to model baseline disease progression in patients who only receive CT. Furthermore, the sponsor's implementation of the natural history of disease allowed disease progression beyond the maximum possible mSASSS. Collectively, the modelled natural history of the disease is uncertain.

- **Uncertain mapping of BASFI score to disease management costs:** The generalizability of the data source underlying the disease management cost algorithm (which excludes the cost of biologic treatment) used by the sponsor is uncertain as it is based on the costs collected for an international cohort of Dutch, Belgian, and French patients between 1996 and 1997.[22] Although the algorithm was converted and inflated to output 2018 Canadian dollars,[6] the submitted models' estimates of disease management costs are based on an outdated context before the availability of multiple biologic treatments more than 20 years ago. It is also unclear to what extent these international disease management cost estimates reflect Canadian disease management costs.

CADTH Common Drug Review Reanalyses

To address some of the identified limitations, CADTH conducted the following reanalyses:

Biologic-naive population:

1. Analysis of the sponsor's ITC efficacy data for BASDAI 0, BASDAI, and BASFI based on the 80 mg IXE initial dose subgroup from the COAST-V trial was conducted. According to the clinical expert consulted by CADTH, the 160 mg IXE initial dose is not expected to be used in the biologic-naive population.
2. Erelzi, another etanercept biosimilar, was added as a comparator. Model parameters for this comparator were assumed to be equivalent to Brenzys, except for the price, for which the Ontario Drug Benefit program listed as $255 per 50 mg unit.[14]
3. Probabilistic analysis was conducted with 5,000 iterations (increased from 2,000 iterations in the sponsor's base case) to ensure stable model results.
4. An alternative utility algorithm from the sponsor based on the EQ-5D-5L measure was incorporated. The algorithm was based on a regression analysis of BASDAI, BASFI, and EQ-5D-5L end points from the COAST-V trial.

TNFi-experienced population:

1. Probabilistic analysis was conducted with 5,000 iterations (increased from 2,000 iterations in the sponsor's base case) to ensure stable model results.
2. The EQ-5D-3L utility algorithm from the biologic-naive population model was incorporated in the TNFi-experienced population model. The EQ-5D-3L utility algorithm for the TNFi-experienced population did not match the clinical expectation that BASDAI is negatively correlated with health utility values. The utility algorithm from the biologic-naive population model was selected as this algorithm has a positive relationship between BASDAI and health utility values. Furthermore, although the algorithm allows utility values to be potentially higher than 0.885, the highest reported mean EQ-5D-3L health state utility value observed in the general Canadian population,19 it does not allow the utility value to exceed one, the conceptual maximum value which reflects perfect health.
3. An alternative utility algorithm based on the EQ-5D-5L utility algorithm from the biologic-naive population model was incorporated in the TNFi-experienced population model.

In the CADTH base case, for the biologic-naive population, IXE was associated with 0.01 incremental QALYs at an additional cost of $6,477 compared to adalimumab, resulting in an ICER of $973,100 per QALY gained (Table 4). Only IXE, adalimumab, secukinumab, and CT remained on the cost-effectiveness efficiency frontier. At a WTP threshold of $50,000 per QALY, IXE had a 0.1% probability of being the optimal treatment. A price reduction of more than 44% is required for IXE to achieve an ICER less than $50,000 per QALY gained. In the TNFi-experienced population, IXE was associated with 0.32 incremental QALYs at an additional cost of $22,882 compared to CT, resulting in an ICER of $70,448 per QALY gained (Table 5). At a WTP threshold of $50,000 per QALY, IXE had a 26% probability of being the optimal treatment. A price reduction of more than 16% is required for IXE to achieve an ICER of less than $50,000 per QALY gained.

Table 4: CADTH Reanalysis for Biologic-Naive Patients (Sequential Analysis Results)

Analysis	Comparator	Total cost ($)	Total QALYs	Incremental cost ($)	Incremental QALYs	Sequential ICER ($/QALY)
Sponsor's base case	CT	366,993	18.48	-	-	Reference
	Secukinumab	379,679	18.94	12,686	0.46	27,368
	Biosimilar etanercept (Brenzys)	391,026	18.96	11,347	0.02	Extendedly dominated
	Adalimumab	410,495	18.99	19,468	0.03	Extendedly dominated
	Ixekizumab	***418,871***	***19.01***	***8,377***	***0.03***	***536,001***
	Etanercept	422,061	18.97	1,353	-0.05	Dominated
1. Probabilistic analysis with 5,000 iterations	CT	369,253	18.48	-	-	Reference
	Secukinumab	381,610	18.95	12,357	0.47	26,430
	Biosimilar etanercept (Brenzys)	392,859	18.96	11,239	0.01	Extendedly dominated
	Adalimumab	412,414	18.99	19,555	0.03	Extendedly dominated
	Ixekizumab	***420,879***	***19.03***	***8,465***	***0.03***	***524,227***
	Etanercept	422,061	18.97	1,182	-0.06	Dominated
2. Efficacy associated with ixekizumab 80 mg initial dose subgroup.	CT	366,993	18.48	-	-	Reference
	Secukinumab	379,679	18.94	12,686	0.46	27,368
	Biosimilar etanercept (Brenzys)	391,026	18.96	11,347	0.02	628,722
	Adalimumab	410,495	18.99	19,468	0.03	699,324
	Ixekizumab	***416,867***	***18.99***	***6,372***	***0.00***	***Dominated***
	Etanercept	420,177	18.96	3,310	-0.02	Dominated
3. Addition of biosimilar etanercept Erelzi	CT	366,993	18.48	-	-	Reference
	Secukinumab	379,679	18.94	12,686	0.46	27,368
	Biosimilar etanercept (Brenzys)	391,026	18.96	11,347	0.02	Extendedly dominated
	Biosimilar etanercept (Erelzi)	391,115	18.95	89	0.00	Dominated
	Adalimumab	410,495	18.99	19,380	0.03	Extendedly dominated
	Ixekizumab	***418,871***	***19.01***	***8,377***	***0.03***	***536,001***
	Etanercept	420,177	18.96	1,306	-0.05	Dominated
4. EQ-5D-5L utility algorithm	CT	366,993	19.01	-	-	Reference
	Secukinumab	379,679	19.56	12,686	0.55	23,013
	Biosimilar etanercept (Brenzys)	391,026	19.58	11,347	0.01	Extendedly dominated
	Adalimumab	410,495	19.61	19,468	0.03	Extendedly dominated
	Ixekizumab	***418,871***	19.65	***8,377***	0.04	**459,657**
	Etanercept	420,177	19.58	1,306	-0.07	Dominated
CADTH Base Case						
	CT	369,253	19.01	-	-	Reference

Analysis	Comparator	Total cost ($)	Total QALYs	Incremental cost ($)	Incremental QALYs	Sequential ICER ($/QALY)
Reanalyses 1, 2, 3, and 4	Secukinumab	381,610	19.56	12,357	0.55	22,353
	Biosimilar etanercept (Brenzys)	392,859	19.58	11,249	0.01	Extendedly dominated
	Biosimilar etanercept (Erelzi)	393,033	19.58	175	0.00	Extendedly dominated
	Adalimumab	412,414	19.61	19,381	0.03	662,007
	Ixekizumab	***418,891***	***19.62***	***6,477***	***0.01***	***973,100***
	Etanercept	422,061	19.58	3,170	-0.04	Dominated

CT = conventional therapy; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 5: CADTH Reanalysis for TNF Inhibitor-Experienced Patients (Sequential Analysis Results)

Analysis	Comparator	Total cost ($)	Total QALYs	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
Sponsor's base case	CT	418,453	13.61	—	—	Reference
	Ixekizumab	***441,521***	***14.05***	***23,068***	***0.44***	***52,122***
1. Probabilistic analysis with 5,000 iterations	CT	421,606	13.60	—	—	Reference
	Ixekizumab	***444,488***	***14.04***	***22,882***	***0.44***	***51,744***
2. Biologic-naive EQ-5D-3L utility algorithm	CT	418,453	16.35	—	—	Reference
	Ixekizumab	***441,521***	***16.62***	***23,068***	***0.27***	***84,118***
3. Biologic-naive EQ-5D-5L utility algorithm	CT	418,453	16.68	—	—	Reference
	Ixekizumab	***441,521***	***17.01***	***23,068***	***0.32***	***71,027***
CADTH Base Case						
Reanalyses 1 and 3	CT	421,606	16.71	—	—	Reference
	Ixekizumab	***444,488***	***17.04***	***22,882***	***0.32***	***70,448***

CT = conventional therapy; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Table 6: CADTH Reanalysis Price Reduction Scenarios–Biologic-Naive Population

ICERs ($/QALY gained) of ixekizumab versus AS treatments included in the model[a]		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
Submitted	If λ < $27,368 CT is optimal If $27,368 < λ < $536,001, secukinumab is optimal If λ > $536,001, ixekizumab is optimal	If λ < $22,353, CT is optimal If $22,353 < λ < $662,007, secukinumab is optimal If $662,007 < λ < $973,100, adalimumab is optimal If λ > $973,100, ixekizumab is optimal
10% reduction	If λ < $27,368, CT is optimal If $27,368 < λ < $426,062, secukinumab is optimal If λ > $426,062, ixekizumab is optimal	If λ < $22,353, CT is optimal If $22,353 < λ < $555,523, secukinumab is optimal If λ > $555,523, ixekizumab is optimal
20% reduction	If λ < $27,368, CT is optimal If $27,368 < λ < $316,123, secukinumab is optimal If λ > $316,123, ixekizumab is optimal	If λ < $22,353, CT is optimal If $22,353 < λ < $410,107, secukinumab is optimal If λ > $410,107, ixekizumab is optimal

ICERs ($/QALY gained) of ixekizumab versus AS treatments included in the model[a]		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
30% reduction	If λ < $27,368, CT is optimal If $27,368 < λ < $206,185, secukinumab is optimal If λ > $206,185, ixekizumab is optimal	If λ < $22,353, CT is optimal If $22,353 < λ < $264,691, secukinumab is optimal If λ > $264,691, ixekizumab is optimal
40% reduction	If λ < $27,368, CT is optimal If $27,368 < λ < $96,246,secukinumab is optimal If λ > $96,246, ixekizumab is optimal	If λ < $22,353, CT is optimal If $22,353 < λ < $119,274, secukinumab is optimal If λ > $119,274, ixekizumab is optimal
44% reduction	If λ < $27,368, CT is optimal If $27,368 < λ < $52,270, secukinumab is optimal If λ > $52,270, ixekizumab is optimal	If λ < $22,353, CT is optimal If $22,353 < λ < $61,108, secukinumab is optimal If λ > $61,108 ixekizumab is optimal
45% reduction	If λ < $27,368, CT is optimal If $27,368 < λ < $41,277, secukinumab is optimal **If λ > $41,277, ixekizumab is optimal**	If λ < $22,353, CT is optimal If $22,353 < λ < $46,566, secukinumab is optimal **If λ > $46,566, ixekizumab is optimal**

AS = ankylosing spondylitis; CT = conventional therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[a] The sponsor's model excluded biosimilar etanercept Erelzi, certolizumab pegol, golimumab, and infliximab. CADTH reanalysis added biosimilar etanercept Erelzi.

Table 7: CADTH Reanalysis Price Reduction Scenarios–TNF Inhibitor-Experienced Population

ICERs ($/QALY gained) of ixekizumab versus CT		
Price	**Base-case analysis submitted by sponsor**	**Reanalysis by CADTH**
Submitted	52,122	70,448
10% reduction	42,852	57,801
16% reduction	33,581	50,213
17% reduction	31,727	**48,948**

CT = conventional therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

To explore the concerns associated with the remaining structural and parametric uncertainties, the following sensitivity analyses were conducted.

Biologic-naive and TNFi-experienced populations:

S1. An alternative assumption regarding the cessation of BASFI response was explored due to the uncertainty associated with the base-case assumption that at treatment discontinuation, BASFI score would increase by the initial amount that decreased upon treatment response. BASFI was instead assumed to increase beyond the initial amount decreased at treatment response, to a level that would reflect more aggressive disease progression that would occur without the use of biologics.

S2. AS was not assumed to contribute to additional mortality beyond the general population rate. This more conservative assumption was explored as the AS-specific mortality in the model was sourced from international data that was partly collected from an outdated period that reflects a treatment environment prior to the availability of multiple biologic treatments.

S3. An alternative utility algorithm based on the EQ-5D-3L utility algorithm from the biologic-naive population model was incorporated instead of the utility algorithm based on the EQ-5D-5L.

S4. The duration of the initial treatment period was standardized to 12 weeks for all comparators. This varied between 12 weeks to 16 weeks in the base-case analysis.

Only for the biologic-naive population:

S5. Additional lines of biologic treatment were considered after failure or discontinuation from the first-line biologic treatment. In the absence of appropriate treatment sequence data, the selection of second-line biologic therapies was informed by IQVIA PharmaStat market share data[23] and a clinical expert consulted by CADTH. For the majority of the patients who started on a biologic treatment, adalimumab was assumed to be the second-line biologic treatment as it currently holds the largest market share in Canada. For patients that started on adalimumab, etanercept was selected as the second-line biologic treatment as although it had a similar market share as infliximab, patients would prefer subcutaneous injection over intravenous infusion according to the clinical expert consulted by CADTH. Patients were assumed to switch to CT after failing or discontinuing the assumed second-line biologic treatment. For patients who started on CT, CT was assumed to be continued as patients starting on CT were assumed to be ineligible to receive biologic treatment.

Cost-effectiveness results remained stable in most scenarios with the exception of analysis S1 (Table 15 and Table 16). In both the biologic-naive and TNFi-experienced populations, analysis S1 increased the ICER associated with IXE to $1,548,526 per QALY gained compared with adalimumab in the biologic-naive population and $84,334 per QALY gained compared with CT in the TNFi-experienced population).

Issues for Consideration

- Given the confidential nature of the negotiated effective price for pharmaceuticals, CADTH is unable to assess the impact of potentially lower prices of comparators or IXE (as previously recommended by CDEC for other indications) on the results.
- An adalimumab biosimilar Hadlima[24] has been approved by Health Canada but is not yet marketed. Its availability may affect the results of the analysis.

Patient Input

Input was received from the Canadian Spondylitis Association, Arthritis Consumer Experts, Canadian Arthritis Patient Alliance, and the Arthritis Society. None of the patients surveyed by these organizations reported experience with IXE. However, the patients expressed a desire for more treatment options that reduce disease symptoms, progression, and side effects, while increasing their ability to participate in employment and carry out activities of daily living.

Specifically, the patients reported limited ability to participate in activities of daily living and social activities due to issues with pain, mobility, fatigue, and sleep. These aspects may have been captured to an extent in the pharmacoeconomic review through the EQ-5D-5L and EQ-5D-3L health-related quality of life measures used in the submitted pharmacoeconomic models, as these measures specifically capture five dimensions of health including pain/discomfort, anxiety/depression, mobility, usual activities, and self-care.[25]

The patients also cited side effects with currently available treatments as concerns, especially with long-term use of corticosteroids such as osteoporosis, glaucoma and cataracts, osteonecrosis, skin changes, heart disease, and stroke, which have not been specifically captured in the pharmacoeconomic model. The patients also mentioned

infection-associated side effects of biologic treatments, which the pharmacoeconomic model captured as episodes of serious infections.

Conclusions

In biologic-naive adults with active AS who have inadequate response or intolerance to CT, CADTH estimated that IXE would be associated with an ICER of $973,100 per QALY gained compared to adalimumab. In the TNFi-experienced population, IXE was associated with an ICER of $70,448 per QALY gained compared to CT. Based on CADTH reanalyses, price reductions of more than 44% and more than 16% would be required for IXE to be the optimal intervention at a WTP threshold of $50,000 per QALY gained in biologic-naive patients and TNFi-experienced patients respectively.

However, considerable uncertainty remains in this analysis given the identified limitations that could not be addressed, including uncertain comparative effectiveness (exclusion of relevant comparators and issues with the sponsor's ITC) and uncertain generalizability of the modelled natural history, health utility algorithm, and disease management costs. Of note, the cost-effectiveness of IXE is likely to be affected by its relationship to other relevant comparators, and this relationship remains unknown as the analyses excluded relevant comparators such as certolizumab pegol, golimumab, and infliximab. CADTH notes that while the annual cost of IXE ranges between $20,569 to $22,151, the annual cost of the other interleukin inhibitor biologic, secukinumab, ranges between $9,973 to $13,298 (Appendix 1).

Appendix 1: Cost Comparison

The comparators presented in Table 8 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice as opposed to actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are sponsor 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 8: CDR Cost Comparison Table of Drugs for Ankylosing Spondylitis

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Annual treatment cost ($)
Ixekizumab (Taltz)	**80 mg/1.0 mL**	**Pre-filled syringe or auto-injector**	**1,582.2369[a]**	**80 mg SC injection q.4.w.**	**20,569**
				160 mg SC injection as the initial dose, followed by 80 mg SC injection q.4.w.[*]	**First year: 22,151 Subsequent years: 20,569**
Biologic disease-modifying antirheumatic drugs					
Adalimumab (Humira)	40 mg/0.8 mL	Vial, pre-filled syringe, or pen Pre-filled syringe or pen	769.9700	40 mg q.2.w. SC injection	20,019
Certolizumab pegol (Cimzia)	200 mg/mL	Single-use pre-filled syringe or auto-injector	664.5100	400 mg SC injection at weeks 0, 2, and 4, then 200 mg q.2.w.or 400 mg q.4.w.	18,606 to 19,271
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)	21,105
	50 mg/mL	Pre-filled syringe or auto-injector	405.9850		21,111
Etanercept SEB (Brenzys)	50 mg/mL	Pre-filled syringe or auto-injector	254.0000	50 mg weekly	13,208
Etanercept SEB (Erelzi)	25 mg/0.5 mL 50 mg/mL	Pre-filled syringe or auto-injector	127.5000 255.0000	50 mg weekly (one 50 mg injection or two 25 mg injections on the same day or 3 or 4 days apart)	13,260
Golimumab (Simponi)	50 mg/0.5 mL 100 mg/mL	Pre-filled syringe or auto-injector	1,555.17[b]	50 mg SC injection once a month (on the same date)	18,662
Golimumab (Simponi IV)	50 mg/4 mL	Vial	17.5900 per mL[c]	2 mg/kg IV infusion at weeks 0 and 4, then q.8.w.	1,266 to 1,689

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Annual treatment cost ($)
Infliximab (Remicade)	100 mg/vial	Vial	987.5600	5 mg/kg initial dose followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter	*Maintenance dose q.8.w.* First year: 31,602 Subsequent years: 23,701 to 27,652 *Maintenance dose q.6.w.* First year: 39,502 Subsequent years: 31,602 to 35,552
Infliximab SEB (Inflectra)	100 mg/vial	Vial	525.0000	5 mg/kg initial dose followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter	*Maintenance dose q.8.w.* First year: 16,800 Subsequent years: 12,600 to 14,700 *Maintenance dose q.6.w.* First year: 21,000 Subsequent years: 16,800 to 18,900
Infliximab SEB (Renflexis)	100 mg/vial	Vial	493.0000	5 mg/kg initial dose followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter	*Maintenance dose q.8.w.* First year: 15,776 Subsequent years: 11,832 to 13,804 *Maintenance dose q.6.w.* First year: 19,720 Subsequent years: 15,776 to 17,748
Secukinumab (Cosentyx)	150 mg/mL	Vial, pre-filled syringe, or pen	831.1100	150 mg by SC injection at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance dosing	First year: 13,298 Subsequent years: 9,973

IV = intravenous; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.6.w. = every 6 weeks; q.8.w. = every 8 weeks; SC = subcutaneous; SEB = subsequent entry biologic.

Note: All prices do not include costs of product dispensing, dose preparation, or administration. The calculated doses are based on the product monograph where available. When multiple formulations were available, the least expensive type was used to calculate costs. All injected comparators are assumed to be used as single-use vials with leftover product being wasted. A year was assumed to consist of 52 weeks. Annual drug costs were based on patients with an assumed weight of 70 kg.

*Limited data also suggests that some TNF inhibitor-experienced patients with ankylosing spondylitis may benefit from a 160 mg starting dose.

[a] Based on the sponsor's pharmacoeconomic submission.[3]

[b] Price only available up to two decimal points.[26]

[c] Saskatchewan Drug Plan (October 2019).[27]

Sources: Ontario Drug Benefit Formulary,[14] including the Exceptional Access Program (accessed October 2019)[26] unless otherwise indicated.

Appendix 2: Additional Information

Table 9: Submission Quality

Description	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?			X
Comments	The submitted models included an excessive amount of Visual Basic for Applications (VBA) code that was not used in the analyses and provided an unnecessary barrier to understanding the model calculations and to conducting reanalyses. Derivation of some input values were not clearly described.		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?			X
Comments	The results and input values in the submitted models did not match the results and input values in the submitted results.		

Table 10: Author Information

Authors of the pharmacoeconomic evaluation submitted to CDR

☐ Adaptation of global model/Canadian model done by the sponsor

☒ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor

☐ 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 3: Summary of Other Health Technology Assessment Agency Reviews of Drug

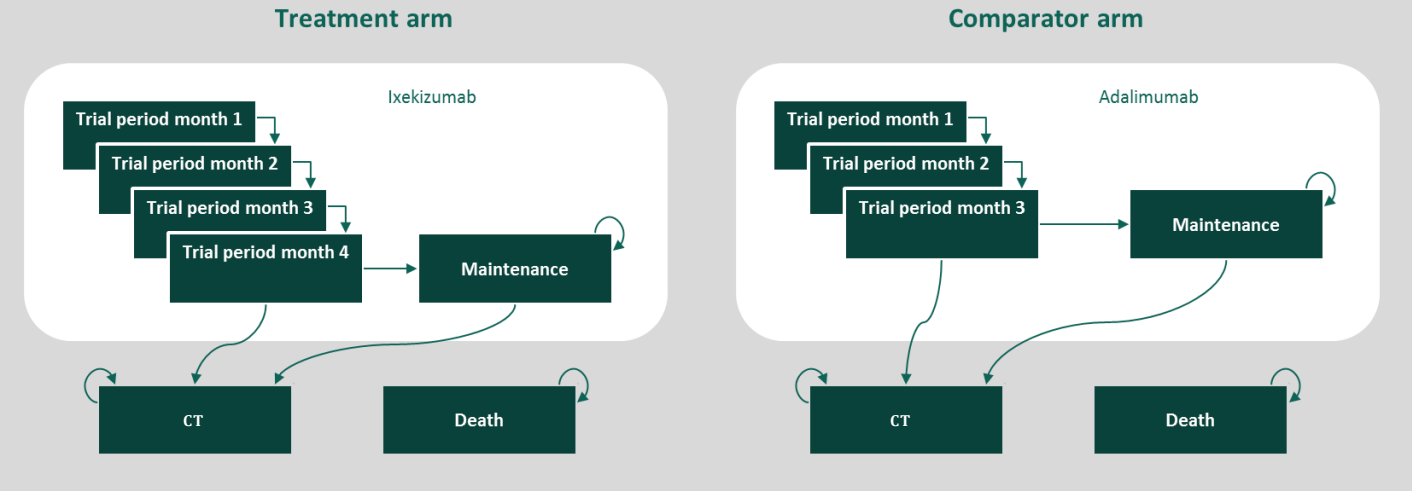
No other health technology assessment agencies have reviewed IXE for the requested CDR indication. IXE has been previously reviewed by NICE,[28,29] Institut national d'excellence en santé et en services sociaux (INESSS),[30,31] the Scottish Medicines Consortium (SMC),[32,33] and the Pharmaceutical Benefits Advisory Committee (PBAC)[34,35] for the indication of plaque psoriasis and psoriatic arthritis.

Appendix 4: Reviewer Worksheets

Sponsor's Model Structure

The modelled biologic-naive and TNFi-experienced populations matched the baseline characteristics of the average patient in the sponsor's COAST-V[7] and COAST-W[8] trials respectively.[6] Patients who received a biologic treatment began the model in a short-term variable biologic treatment trial period (ranging from 12 weeks for adalimumab, etanercept, and biosimilar etanercept, to 16 weeks for IXE and secukinumab) to assess BASDAI 50 response (Figure 1). Patients who responded would move to a long-term maintenance period and those who did not respond would move to a CT state. Patients that discontinued treatment (11% annual biologic treatment discontinuation rate assumed) during the long-term maintenance period would also move to the CT state. The long-term maintenance and CT states were modelled as four-week cycles. Treatment-dependent probabilities of BASDAI 50 response were informed by the sponsor's indirect treatment comparison (ITC)[9] for the biologic-naive population and by the COAST-W trial[8] for the TNFi-experienced population. Patients who received CT stayed on CT regardless of response until end of time horizon or death.

Figure 1: Schematic of Modelling One Treatment Line



CT = conventional therapy.

Note: This figure shows the model structure for patients receiving active treatment (using ixekizumab as an example) and for the comparator CT sequence. Arrows to death were removed for simplification; patients can transition to death state from any health state. The treatment trial period can vary in duration by treatment.
Source: Sponsor's pharmacoeconomic submission.[6]

Table 11: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Baseline age, weight, and sex distribution for the biologic-naive and TNFi-experienced patients reflected the average patient in the COAST-V[7] and COAST-W[8] trials respectively.	Appropriate according to the clinical expert consulted by CADTH.
Efficacy	Biologic-naive population analysis: Sponsor's ITC.[9] Results from a Bayesian fixed-effects analysis were used to derive BASDAI 50 response rate and treatment- and response-specific changes in BASDAI and BASFI scores. TNFi-experienced population analysis: Ixekizumab and placebo arm results from the sponsor's COAST-W trial[8] was used to inform BASDAI50 response rate, BASDAI change, and BASFI change. For the biologic-naive and TNFi-experienced populations, the sponsor used data based on a population that included patients with initial ixekizumab doses of 80 mg and 160 mg.	Uncertain. According to the CADTH clinical reviewers, there was insufficient information about the ITC methodology and the quality of the included studies, limiting the ability to assess clinical heterogeneity of the studies and rendering the credibility of the findings uncertain. Additionally, as the ITC findings reflect trial results up to 12 to 16 weeks of treatment, it is uncertain whether the comparative efficacy estimated by the ITC would be durable over a longer term. Furthermore, the ITC did not include all relevant comparators such as certolizumab pegol, golimumab, and infliximab. BASDAI 50 was a secondary end point in the COAST-W trial and was not controlled for multiplicity. According to CADTH clinical reviewers, the statistical significance of the BASDAI 50 results therefore remains uncertain. It is also uncertain whether the results would be durable over a longer term as the extension phase results at week 52 were limited by the lack of comparison to placebo. Inappropriate. The product monograph[1] recommends an 80 mg initial dose for the biologic-naive population. Efficacy for this population should be based on the 80 mg initial dose subgroup results.
Natural history	Assumptions based on the UK AS economic model.[15] Radiographic disease progression rate based on the mSASSS from the OASIS longitudinal patient cohort[21] was converted to BASFI using an algorithm by Landewe and van Tubergen, 2015.[36] Based on this algorithm, non-responders to biologics and other patients in the CT state experienced an increase in BASFI score at 0.082 units per year. Patients remaining in the maintenance state were assumed to benefit from biologics and experienced an increase in BASFI score at a reduced rate of 0.034 units per year, based on an observational study that found a lower rate of radiographic progression in patients who	Uncertain. The progression rates were based on 12-year longitudinal data from the OASIS cohort–an AS patient cohort from the Netherlands, Belgium, and France that began in 1996.[21] Whether the international OASIS longitudinal cohort reflects the modern Canadian AS population who receive CT is unknown. As the cohort data included a period when bDMARDs were available, the data may underestimate progression in patients who only receive CT. This bias may also persist in the model's estimate of disease progression in bDMARD responders as the relative ratio was applied to the baseline disease progression rate without controlling for the underlying bias.

Data input	Description of data source	Comment
	used TNFis compared to CT (relative ratio of 0.42).[37]	Additionally, the sponsor's approach allowed the BASFI increase due to radiographic progression to exceed the maximum achievable mSASSS score (i.e., 72[36]). The sponsor modelled patients to gain more than 4.104 in BASFI score over a lifetime due to radiographic progression, which would unrealistically imply that the mSASSS score in these patients had increased by more than 72 points.
Utilities	The sponsor conducted a linear regression analysis of BASFI, BASDAI, and EQ-5D-5L data from the intention-to-treat population of the COAST-V trial[7] (for the biologic-naive population) and the COAST-W trial[8] (for the TNFi-experienced population) to map BASFI and BASDAI to EQ-5D-3L-based health utility values. For the analysis, the EQ-5D-5L scores from the COAST-V and COAST-W trials were converted to EQ-5D-3L scores based on an algorithm from van Hout et al. (2012).[20] The EQ-5D utilities were valued based on Canadian EQ-5D-5L and EQ-5D-3L preference sets.[19,38]	Inappropriate. The sponsor's approach does not satisfy construct validity. The intercept of the EQ-5D-3L and EQ-5D-5L models are higher than the highest mean EQ-5D-3L health state utility value reported for Canadians (0.885[19]). For the TNFi-experienced population, a person with a low BASFI and BASDAI score may have a health utility score larger than the maximum conceptual health utility value of one (perfect health). Additionally, the positive correlation between BASDAI and health utility values modelled in the regression equation for the TNFi-experienced population does not match clinical expectations. According to the clinical expert consulted by CADTH, health utility is expected to be negatively correlated to BASDAI scores. The regression equation for the biologic-naive population appropriately modelled a negative correlation between BASDAI and health utility values. It is also uncertain whether it was necessary to map from EQ-5D-5L to EQ-5D-3L. The EQ-5D-5L regression equations was more sensitive to changes in BASDAI and BASFI in the biologic-naive population, and to changes in BASFI in the TNFi-experienced population. The sponsor's sensitivity analysis demonstrated the impact of this change on the ICER.
Adverse events (serious infection)	Serious infection rates were sourced from the EMA summary of product characteristics for ixekizumab, adalimumab, etanercept, and secukinumab.	Acceptable. However, the trial data incorporated into the EMA documents are unlikely to capture the full effects of adverse events due to their short duration. It is uncertain whether the incorporated adverse events would reflect AS treatment experience in the long run.
Mortality	Canadian age-specific mortality tables, corrected for an AS standardized mortality ratio of 1.38 for women and 1.63 for men as per Bakland et al. (2011).[11]	Uncertain. The Bakland et al. (2011) study was based on a cohort of Norwegian patients that were followed from 1977 until 2009.[11] According to the clinical expert consulted by CADTH, data collected before the availability of multiple biologics may overestimate

Data input	Description of data source	Comment
		disease progression and mortality. Furthermore, the generalizability of data from an international cohort is uncertain.
Discontinuation	The same annual withdrawal rate was assumed for all biologics (11% per year). The input on discontinuation was based on a UK AS economic model.[15]	Appropriate according to the clinical expert consulted by CADTH.
Resource use and costs		
Drug	Cost of ixekizumab provided by the sponsor.[3] Cost of relevant comparators from Ontario Drug Benefit formulary.[14]	Appropriate Appropriate
Resource use	Biologic treatment resources used for monitoring and follow-up were based on clinical expert input and comprised of a specialist visit and a chest radiograph, and were assumed to be the same for all biosimilars. Unit costs for biologic treatment-related resource use and drug administration were derived from the 2016 Schedule of Benefits for Physician Services by the Ministry of Health and Long-Term Care[13] and were inflated to 2018 costs. Sponsor adapted the cost algorithm from the 2016 UK AS economic model,[15] which converts BASFI scores to non-biologic treatment-related disease management costs (i.e., excludes biologic drug acquisition, administration, monitoring, and adverse event costs). The algorithm was based on a regression of disease management costs in the international OASIS cohort.[22] The cost coefficient in this algorithm, originally in 2016 British pounds, was converted and inflated to 2018 Canadian dollars.[6]	Acceptable Inappropriate. Ontario schedule of benefit fees are not inflated on an annual basis and are instead subject to periodic updates based on consultations between the Ontario Health Insurance Plan and the Ontario Medical Association. Uncertain. The cost algorithm was based on two-year cost data from the Netherlands, France, and Belgium that recruited patients between 1996 and 1997.[22] The generalizability of the cost algorithm derived from this outdated international cost data are unknown.
Adverse event	Weighted average of the following adverse event costs were used to approximate the cost of a serious infection (17% each): • septicemia • bronchopneumonia • kidney or urinary tract infection • major infection • unspecified acute lower respiratory infection • chronic obstructive pulmonary disease or bronchitis.	Uncertain. Acceptable as a simplifying assumption.

Data input	Description of data source	Comment
	These costs were sourced from Ontario Case Costing Initiative.[12]	Appropriate.

AS = ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; bDMARD = biologic disease-modifying antirheumatic drug; CT = conventional therapy; EMA = European Medicines Agency; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; OASIS = outcome in ankylosis spondylitis international study; TNFi = tumour necrosis factor inhibitor.

Table 12: Sponsor's Key Assumptions

Assumption	Comment
Non-responders or patients who discontinue treatment do not try other bDMARDs.	Inappropriate. According to the clinical expert consulted by CADTH, patients who discontinue ixekizumab are likely to switch to another biologic. As responders to the subsequent treatment are likely to have lower BASDAI and BASFI scores, the BASDAI and BASFI difference between ixekizumab and other comparators may be overestimated, leading to cost-effectiveness results in favour of ixekizumab.
Treatment does not affect mortality.	Acceptable.
CT was not costed.	Acceptable as these costs are likely captured in the sponsor's BASFI-based disease management costing approach.
Comparators with subcutaneous injections were assumed to be administered by a health professional for the first administration.	Acceptable
Efficacy and safety of biosimilar etanercept were assumed to be equal to etanercept.	Acceptable
Tuberculosis Heaf test was assumed to not be reimbursed by a public health care payer.	Acceptable
BASDAI score reverts to baseline value upon treatment discontinuation due to a loss of response or a severe adverse event.	Uncertain. While responders who discontinued treatment may progress to the baseline BASDAI score within a month of discontinuation as modelled, it is uncertain whether this would reflect the average experience of the patients. In practice patients would likely switch to another biologic treatment.
Upon treatment discontinuation, BASFI score increases by the same amount as decreased during the initial response.	Uncertain. Alternative assumptions were explored as scenario analyses.
BASFI score increase due to radiographic progression was allowed to exceed the range that is possible on the mSASSS.	Inappropriate
Response definition was based on a BASDAI 50 criteria.	Acceptable. According to the clinical expert consulted by CADTH, BASDAI 50 is used both clinically and in provincial drug reimbursement criteria. However, the response criteria vary across jurisdictions and may also consider other endpoints including BASFI, health assessment questionnaire, return to work, or a two-point decrease in the pain visual analogue scale component of BASDAI. It is uncertain how efficacy based on different response criteria would impact the cost-effectiveness results.
Adverse events were not assumed to decrease health utility.	Uncertain. Given the small incremental QALYs between comparators, rare but serious infections may impact cost-effectiveness outcomes.
Adverse events were not assumed to occur in CT.	Acceptable as a conservative assumption.

bDMARD = biologic disease-modifying antirheumatic drug; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CT = conventional therapy; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; QALY = quality-adjusted life-year.

Sponsor's Sensitivity Analyses

The results for the sponsor's sensitivity analysis based on the efficacy data for the IXE 80 mg initial dose subgroup in the biologic-naive population is reported in Table 13:

Table 13: Summary of Sequential Analysis Results of the Sponsor's Base Case for Biologic-Naive Patients (Ixekizumab 80 mg Initial Dose Subgroup)

Drug	Total costs ($)	Total QALYs	Incremental cost ($)	Incremental QALYs	Incremental cost per QALY ($)
CT	368,879	18.48	—	—	Reference
Secukinumab	381,320	18.95	12.441	0.47	26,663
Biosimilar etanercept	392,587	18.96	11.267	0.01	Extendedly dominated
Adalimumab	412,199	18.99	19.611	0.03	774,120
Ixekizumab	**420,417**	18.99	**6,201**	**0.01**	**1,229,765**
Etanercept	421,770	18.97	3,370	–0.03	Dominated

CT = conventional therapy; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[6]

CADTH Common Drug Review Reanalyses

Detailed TNFi-Experienced Population Base-Case Results

Table 14: Detailed TNF Inhibitor-Experienced Population Base-Case Results

Outcome	Ixekizumab	CT	Incremental difference
Costs ($)	**444,488**	**421,606**	**22,882**
Treatment[a]	41,079	0	41,079
Administration[a]	27	0	27
Physician visits[a]	703	0	703
Monitoring[a]	23	0	23
Adverse events[a]	302	0	302
Disease management	402,354	421,606	19,252
QALYs	**17.04**	**16.71**	**0.32**
Incremental cost per QALY ($)	**70,448**	Reference	—

CT = conventional therapy; QALY = quality-adjusted life-year.

[a] These reported costs only pertain to biologic treatments.

Sensitivity Analyses

To explore the concerns associated with the remaining structural and parametric uncertainties, the following sensitivity analyses were conducted by CADTH:

Biologic-naive and TNFi-experienced populations:

S1. An alternative assumption regarding the cessation of BASFI response was explored due to the uncertainty associated with the base-case assumption that at treatment discontinuation, BASFI score would increase by the initial amount that was decreased

at treatment response. BASFI was instead assumed to increase beyond the initial amount decreased at treatment response, to a level that would reflect more aggressive disease progression that would occur without the use of biologics.

S2. AS was not assumed to contribute to additional mortality beyond the general population rate. This more conservative assumption was explored as the AS-specific mortality in the model was sourced from international data that was partly collected from an outdated period that reflects a treatment environment prior to the availability of multiple biologic treatments.

S3. An alternative utility algorithm based on the EQ-5D-3L utility algorithm from the biologic-naive population model was incorporated instead of the utility algorithm based on the EQ-5D-5L.

S4. Duration of initial treatment to assess treatment response was standardized to 12 weeks for all comparators. This varied between 12 weeks to 16 weeks in the base-case analysis.

Only for the biologic-naive population:

S5. Additional lines of biologic treatment were considered after failure or discontinuation from the first biologic treatment. In the absence of appropriate treatment sequence data, the selection of second-line biologic therapies was informed by IQVIA PharmaStat market share data[23] and a clinical expert consulted by CADTH. For the majority of the patients who started on a biologic treatment, adalimumab was assumed to be the second-line biologic treatment as it currently holds the largest market share in Canada. For patients that started on adalimumab, etanercept was selected as the second-line biologic treatment as although it had a market share similar to infliximab, patients would prefer subcutaneous injection over intravenous infusion according to the clinical expert consulted by CADTH. Patients were assumed to switch to CT after failing or discontinuing the assumed second-line biologic treatment. For patients who started on CT, CT was assumed to be continued as patients starting on CT were assumed to be ineligible to receive biologic treatment.

Table 15: CADTH Sensitivity Analyses (Biologic-Naive Population)

	Analysis	Comparator	Cost ($)	QALYs	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
S1	BASFI score increases to natural history at treatment discontinuation instead of reverting back to baseline value	CT	369,253	19.01	—	—	Reference
		Secukinumab	389,372	19.54	20,119	0.53	37,802
		Biosimilar etanercept (Brenzys)	401,640	19.56	12,269	0.01	Extendedly dominated
		Biosimilar etanercept (Erelzi)	401,828	19.56	187	0.00	Dominated
		Adalimumab	420,442	19.59	18,614	0.03	676,942
		Ixekizumab	***427,600***	***19.59***	***7,159***	***0.00***	***1,548,526***
		Etanercept	430,852	19.56	3,251	–0.04	Dominated
S2	No AS-specific mortality	CT	417,964	20.74	—	—	Reference
		Secukinumab	428,970	21.30	11,006	0.57	19,477

	Analysis	Comparator	Cost ($)	QALYs	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
		Biosimilar etanercept (Brenzys)	440,336	21.32	11,366	0.01	Extendedly dominated
		Biosimilar etanercept (Erelzi)	440,511	21.32	174	0.00	Dominated
		Adalimumab	460,326	21.35	19,815	0.03	664,858
		Ixekizumab	***466,699***	***21.36***	***6,373***	***0.01***	***873,656***
		Etanercept	469,986	21.32	3,287	–0.04	Dominated
S3	Biologic-naive EQ-5D-3L utility algorithm	CT	369,252	18.48	—		Reference
		Secukinumab	381,610	18.95	12,357	0.47	26,430
		Biosimilar etanercept (Brenzys)	392,859	18.96	11,249	0.01	Extendedly dominated
		Biosimilar etanercept (Erelzi)	393,033	18.96	175	0.00	Extendedly dominated
		Adalimumab	412,414	18.99	19,381	0.03	752,404
		Ixekizumab	***418,891***	***19.00***	***6,477***	***0.01***	***919,683***
		Etanercept	422,061	18.97	3,170	–0.03	Dominated
S4	12-week initial treatment trial period	CT	369,253	19.01	—		Reference
		Secukinumab	381,339	19.56	12,086	0.55	21,895
		Biosimilar etanercept (Brenzys)	392,859	19.58	11,520	0.02	Extendedly dominated
		Biosimilar etanercept (Erelzi)	393,033	19.58	175	0.00	Dominated
		Adalimumab	412,414	19.61	19,381	0.03	656,265
		Ixekizumab	***417,929***	***19.62***	***5,515***	***0.01***	***929,580***
		Etanercept	422,061	19.58	4,132	–0.04	Dominated
S5	Addition of adalimumab and etanercept as second-line biologic treatments	CT	369,253	19.01	—	—	Reference
		Secukinumab – adalimumab	419,789	20.11	50,536	1.10	45,880
		Biosimilar etanercept (Brenzys) – adalimumab	430,673	20.12	10,884	0.01	Extendedly dominated
		Biosimilar etanercept (Erelzi) – adalimumab	430,861	20.12	188	0.00	Dominated
		Ixekizumab – adalimumab	***456,662***	***20.16***	***25,801***	***0.04***	***794,114***
		Adalimumab – etanercept	459,359	20.13	2,697	–0.03	Dominated
		Etanercept – adalimumab	459,870	20.12	511	–0.01	Dominated

AS = ankylosing spondylitis; BASFI = Bath ankylosing spondylitis functional index; CT = conventional therapy; EQ-5D-3L = EuroQol 5-Dimensions questionnaire 3 levels; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Table 16: CADTH Sensitivity Analyses (TNF Inhibitor-Experienced Population)

	Analysis	Comparator	Cost ($)	QALYs	Incremental cost ($)	Incremental QALYs	ICER ($/QALY)
S1	BASFI score increases to natural history at treatment discontinuation instead of reverting back to baseline value	CT	421,606	16.71	—	—	Reference
		Ixekizumab	***448,284***	***17.03***	***26,678***	***0.32***	***84,334***
S2	No AS-specific mortality	CT	477,957	18.41	—	—	Reference
		Ixekizumab	***500,710***	***18.75***	***22,753***	***0.33***	***68,379***
S3	Biologic-naive EQ-5D-3L utility algorithm	CT	421,606	16.62	—	—	Reference
		Ixekizumab	***444,488***	***16.34***	***22,882***	***0.27***	***83,537***
S4	12-week initial treatment trial period	CT	421,606	16.71	—	—	Reference
		Ixekizumab	***443,526***	***17.04***	***21,920***	***0.32***	***67,683***

AS = ankylosing spondylitis; BASFI = Bath ankylosing spondylitis functional index; CT = conventional therapy; EQ-5D-3L = EuroQol 5-Dimensions questionnaire 3 levels; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

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