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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Upadacitinib (Rinvoq)

(AbbVie)

Indication: For the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

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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
ACR20	20% improvement in the American College of Rheumatology criteria
ACR50	50% improvement in the American College of Rheumatology criteria
ACR70	70% improvement in the American College of Rheumatology criteria
bDMARD	biologic disease-modifying antirheumatic drug
bDMARD-IR	responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs
BSC	best supportive care
CDEC	CADTH Canadian Drug Expert Committee
csDMARD	conventional synthetic disease-modifying antirheumatic drug
csDMARD-IR	responded inadequately or are intolerant to one or more conventional synthetic disease-modifying antirheumatic drugs
EQ-5D	EuroQol 5-Dimensions
HAQ	Health Assessment Questionnaire
HUI-3	Health Utility Index 3
ICUR	incremental cost-utility ratio
JAK	Janus kinase
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
SAE	serious adverse event
SC	subcutaneous
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
WTP	willingness to pay

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Upadacitinib (Rinvoq)
Study question	To develop a cost-utility analysis that compares upadacitinib to other DMARDs available in Canada for the treatment of patients with moderate-to-severe active RA who have responded inadequately or are intolerant to one or more csDMARDs or bDMARDs
Type of economic evaluation	Cost-utility analysis
Target population	Adults with moderate-to-severe RA who have responded inadequately or are intolerant to one or more csDMARDs (csDMARD-IR population) or one or more bDMARDs (bDMARD-IR population)
Treatment	Upadacitinib 15 mg (with or without csDMARD)
Outcome	QALYs
Comparators	• **csDMARD-IR population:** csDMARD, tofacitinib, baricitinib, certolizumab, etanercept (biosimilar), adalimumab, golimumab, infliximab (biosimilar), rituximab, sarilumab, abatacept (IV/SC), tocilizumab (IV/SC) • **bDMARD-IR population:** csDMARD, tofacitinib, baricitinib, certolizumab, golimumab, rituximab, abatacept (IV), sarilumab, tocilizumab (IV)
Perspective	Canadian publicly funded health care payer
Time horizon	5 years
Results for base case	In a sequential analysis: • **csDMARD-IR population:** If a decision-maker's WTP is greater than $107,659 per QALY, upadacitinib + csDMARD is the optimal treatment; upadacitinib monotherapy was extendedly dominated through upadacitinib + csDMARD and etanercept 50 mg + csDMARD • **bDMARD-IR population:** If a decision-maker's WTP is between $104,193 and $303,516 per QALY, upadacitinib + csDMARD is the optimal treatment
Key limitations	• The CADTH clinical review indicated that the magnitude of benefit associated with upadacitinib in the csDMARD-IR population was variable, while the comparative effectiveness for the bDMARD-IR population was associated with high statistical uncertainty. • The methodology to map HAQ scores to HUI-3 utilities is highly uncertain. EQ-5D data were collected in the SELECT clinical trials but not used in the model, which would have been preferred over mapped utilities. • BSC was assumed to include a previously received bDMARD (including JAK inhibitors) as opposed to csDMARDs, after patients failed two prior therapies. • Administration costs of SC and IV treatment were inappropriately applied. • Analyses were not stratified by moderate and severe disease, which may limit decision-makers' ability to interpret or implement the findings not explored.
CADTH estimate(s)	**csDMARD-IR population:** • The preferred option is csDMARD monotherapy if a decision-maker's WTP is below $127,425 per QALY, etanercept 50 mg + csDMARD if the decision-maker's WTP is between $127,425 and $323,344 per QALY, and upadacitinib + csDMARD if a decision-maker's WTP is more than $323,344 per QALY. Upadacitinib monotherapy remained extendedly dominated. • If the WTP is $50,000 per QALY, a 50% to 60% price reduction is required for upadacitinib + csDMARD to be considered cost-effective compared to csDMARD monotherapy. If csDMARD treatment is excluded from analyses, a 30% to 35% price reduction is required for upadacitinib monotherapy and upadacitinib + csDMARD to be considered cost-effective compared to infliximab 3 mg/kg + csDMARD and upadacitinib monotherapy, respectively.

	bDMARD-IR population: • The preferred option is csDMARD monotherapy if a decision-maker's WTP is below $194,423 per QALY, upadacitinib + csDMARD if the decision-maker's WTP is between $194,423 and $231,785 per QALY, and tocilizumab 8 mg/kg + csDMARD if the decision-maker's WTP is more than $231,785 per QALY. • If the WTP is $50,000 per QALY, a 60% to 70% price reduction is required for upadacitinib + csDMARD to be considered cost-effective compared to csDMARD monotherapy. If csDMARD treatment is excluded from analyses, a 5% price reduction is required for upadacitinib + csDMARD to be considered cost-effective compared to baricitinib 2 mg + csDMARD.

bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = responded inadequately or are intolerant to one or more bDMARDs; BSC = best supportive care; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; DMARD = disease-modifying antirheumatic drug; EQ-5D = EuroQol 5-Dimensions; HAQ = Health Assessment Questionnaire; HUI-3 = Health Utility Index 3; JAK = Janus kinase; QALY = quality-adjusted life-year; RA = rheumatoid arthritis; SC = subcutaneous; WTP = willingness to pay.

Note: Extended dominance means that a strategy is more costly and provides fewer QALYs than a linear combination of two other strategies.

Drug	Upadacitinib (Rinvoq)
Indication	For the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Upadacitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs.
Reimbursement request	As per indication; reimburse in a similar manner to biologic DMARDs and targeted synthetic DMARDs for the treatment of moderate-to-severe rheumatoid arthritis.
Dosage form	15 mg extended-release tablets, oral
NOC date	December 23, 2019
Sponsor	AbbVie

DMARD = disease-modifying antirheumatic drug; NOC = Notice of Compliance.

Executive Summary

Background

Upadacitinib is a Janus kinase (JAK) inhibitor (also referred to as a targeted synthetic disease-modifying antirheumatic drug [tsDMARD] in practice), indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate.[1] The recommended dose of upadacitinib is 15 mg daily as monotherapy or combination therapy. At the sponsor-submitted price of $48.68 per 15 mg tablet,[2] the annual treatment cost is $17,770.

The sponsor submitted a cost-utility analysis that considered upadacitinib as initial treatment for moderate-to-severe RA after an inadequate response or are intolerant to either a conventional synthetic disease-modifying antirheumatic drug (csDMARD-IR population) or a biologic disease-modifying antirheumatic drug (bDMARD-IR population).[2] The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a five-year time horizon. Comparators included csDMARDs, bDMARDs, and other tsDMARDs. The pharmacoeconomic submission was based on a Markov model, where treatment response was evaluated using the American College of Rheumatology (ACR) response criteria.[3] The model was composed of four main health states after the evaluation of initial treatment: 20% improvement in ACR criteria (ACR20); 50% improvement in ACR criteria (ACR50); 70% improvement in ACR criteria (ACR70); and lack of adequate treatment response (i.e., did not achieve minimum of ACR20). Patients who had an inadequate response or discontinued treatment owing to a serious adverse event (SAE) could receive a subsequent treatment and transition to any of the previously mentioned health states. If an adequate response was not achieved on subsequent treatment, patients received best supportive care (BSC), the prior therapy (bDMARD or tsDMARD) which patients achieved the best treatment effect. A sponsor-commissioned network meta-analysis (NMA) was submitted and informed the comparative ACR response at weeks 12 and 24. SAEs were incorporated on the basis of an NMA previously conducted by CADTH[4] and updated to include upadacitinib and other missing comparators. Long-term discontinuation was included in the model owing to a loss of treatment effect over time. Health state utility values for ACR response and nonresponse were based on Health Assessment Questionnaire (HAQ) scores mapped to the Health Utility Index 3 (HUI-3) tool.

In the sponsor's base case, upadacitinib + csDMARD was associated with both higher total costs and quality-adjusted life-years (QALYs) when compared to csDMARD monotherapy in both target populations. In the csDMARD-IR population, the preferred option is csDMARD monotherapy if the decision-maker's willingness to pay (WTP) is below $74,979 per QALY, infliximab 3 mg/kg + csDMARD if the decision-maker's WTP is between $74,979 and $80,897 per QALY, etanercept 50 mg + csDMARD if the decision-maker's WTP is between $80,897 and $107,659 per QALY, and upadacitinib + csDMARD if the decision-maker's WTP is more than $107,659 per QALY. In the bDMARD-IR population, the preferred option is a csDMARD if the decision-maker's WTP is below $104,193 per QALY, upadacitinib + csDMARD if the decision-maker's WTP is between $104,193 and $303,516 per QALY, and tocilizumab 8 mg/kg + csDMARD if the decision-maker's WTP is more than $303,516 per QALY. Other treatments were dominated or extendedly dominated.

Summary of Identified Limitations and Key Results

CADTH identified several limitations with the sponsor's pharmacoeconomic submission.

The CADTH Clinical Review Report indicated there was uncertainty in the clinical estimates from the NMA used to derive the cost-effectiveness results; greater uncertainty was reported with the bDMARD-IR population than with the csDMARD-IR population; therefore, cost-effectiveness results in this population should be interpreted with caution. The sponsor used a linear model to map HAQ scores to health state utilities, which does not align with best practices in this area; best practices suggest that a nonlinear or mixture model should be used. Further, the use of mapped values was questionable given the availability of EuroQol 5-Dimensions (EQ-5D) scores from the SELECT clinical trials. Additionally, while the sponsor's simplifying assumption of subsequent treatments does not reflect Canadian clinical practice — clinical expert feedback indicated that the majority of patients would receive more than two bDMARD or tsDMARD treatments prior to receiving BSC - which impacts generalizability, a larger issue was the assumption that treatment effects varied on the basis of prior treatment, which increased uncertainty and may have biased the results. Further, the sponsor overestimated the cost of BSC, with the assumption that patients would receive a prior bDMARD or tsDMARD that achieved the "best treatment effect," which does not align with clinical practice or previous health technology assessments.[5-7] Finally, the sponsor's results were not stratified according to moderate or severe disease, and owing to structural limitations, CADTH could not address this in the economic model, limiting the decision-maker's ability to assess the optimal place in therapy.

Additional limitations included that the administration costs of subcutaneous (SC) and IV treatment were overestimated, the time horizon was short considering the lifetime of RA (five years), and no mortality adjustment for RA patients was considered.

CADTH also identified several corrections required to the model: Updated drug costs and mortality data were identified, and resource use and subsequent treatment efficacy values presented in the report were updated in the model. The CADTH base case reflected these corrections, as well as the following changes based on the aforementioned limitations: RA-specific mortality was incorporated, the costs of csDMARD were used for BSC, treatment administration costs were removed in response to clinical expert feedback that IV costs are incurred by the manufacturers and SC treatments would be self-administered by the patient, equal subsequent treatment efficacy was applied, nonresponders and patients discontinuing treatment returned to baseline HAQ, and a nonlinear mapping equation for HAQ to EQ-5D from Soini et al. was applied.

In CADTH's base case, the incremental cost-utility ratio (ICUR) for upadacitinib + csDMARD increased in both target populations. In the csDMARD-IR population, the preferred option is csDMARD monotherapy if a decision-maker's WTP is below $127,425 per QALY, etanercept 50 mg + csDMARD if the WTP is between $127,425 and $323,344 per QALY, and upadacitinib + csDMARD if the WTP is more than $323,344 per QALY. In this population, upadacitinib monotherapy remained extendedly dominated, while other treatments remained dominated. In the bDMARD-IR population, the preferred option is csDMARD monotherapy if a decision-maker's WTP is below $194,423 per QALY, upadacitinib + csDMARD if the WTP is between $194,423 and $231,785 per QALY, and tocilizumab 8 mg/kg + csDMARD if the WTP is more than $231,785 per QALY. Other treatments remained dominated or extendedly dominated. Scenario analyses that excluded csDMARD as a comparator were also undertaken. Upadacitinib was not cost-effective at a WTP of $50,000 per QALY in these analyses.

Conclusions

The CADTH reanalyses aligned with the sponsor's base-case analyses, indicating that upadacitinib as monotherapy or in combination with a csDMARD is not a cost-effective treatment at conventionally accepted WTP thresholds.

Price reductions can improve the cost-efficiency of upadacitinib + csDMARD in patients with moderate-to-severe RA relative to the reference product (i.e., the least costly alternative):

- csDMARD-IR: If a decision-maker's WTP threshold is $50,000 per QALY, a price reduction of approximately 50% to 60% is required for upadacitinib + csDMARD to be considered cost-effective. If csDMARD treatment is excluded from analyses, a 30% to 35% price reduction is required for upadacitinib monotherapy and upadacitinib + csDMARD to be considered cost-effective compared to infliximab 3 mg/kg + csDMARD and upadacitinib monotherapy, respectively.
- bDMARD-IR: If a decision-maker's WTP threshold is $50,000 per QALY, a price reduction of approximately 60% to 70% is required for upadacitinib + csDMARD to be considered cost-effective. If csDMARD treatment is excluded from analyses, a price reduction of approximately 5% is required for upadacitinib + csDMARD to be considered cost-effective.

However, several limitations were identified that could not be addressed in the submitted model, most notably the inability to explore the cost-effectiveness for moderate or severe RA patients and the need for long-term extension of the time horizon. The cost-effectiveness of the results should be viewed within the context of the clinical findings.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

Overview

The sponsor submitted a cost-utility analysis based on a Markov state-transition model for the initial treatment of moderate-to-severe RA patients who have responded inadequately or are intolerant to one or more csDMARDs (csDMARD-IR population) or bDMARDs (bDMARD-IR population).[2] The analysis was conducted from the Canadian publicly funded health care payer perspective over a five-year time horizon with a three-month cycle (no half-cycle correction was applied). The base case was a probabilistic analysis of 10,000 iterations with costs and benefits discounted 1.5% per annum. General population mortality was applied using Statistics Canada life tables.[8]

The model considered treatment with upadacitinib 15 mg once daily as monotherapy (csDMARD-IR population) or in combination with a csDMARD (csDMARD-IR and bDMARD-IR populations). An overview of comparators is shown in Table 7, which included csDMARDs (i.e., methotrexate, leflunomide, sulfasalazine, hydroxychloroquine), bDMARDs, and tsDMARDs. Comparators were selected on the basis of the current standard of care in Canada for RA and the availability of data in the sponsor-submitted, unpublished NMA.

Markov Model

The Markov model included 12 health states, stratified by initial and subsequent treatments, according to ACR response criteria,[3] as shown in Figure 1. Following treatment initiation, patients were evaluated after three months to assess if a minimum level of response (i.e., at least a 20% improvement in ACR response) was achieved. Patients who achieved a minimum response were assumed to receive continued treatment and could transition to the ACR health states, which include: 20% improvement in ACR criteria (ACR20); 50% improvement in ACR criteria (ACR50); or 70% improvement in ACR criteria (ACR70). Patients experiencing an SAE or a lack of adequate treatment response throughout the modelled time horizon transitioned to a nonresponder health state and initiated subsequent treatment (i.e., bDMARD or tsDMARD) from which they could move to an ACR response or nonresponder health state. If an adequate response was not achieved or patients experienced a discontinuation on the subsequent treatment, the sponsor assumed all patients received BSC, consisting of the previous therapy on which patients achieved the best treatment effect. Patients could transition to death from any health state.

Patient Cohort

Two patient cohorts with moderate-to-severe RA were considered in separate analyses: the csDMARD-IR population and the bDMARD-IR population, as measured by 2010 ACR/ European League Against Rheumatism classification criteria.[9]

Baseline characteristics were based on patients from the SELECT clinical trials, according to the target population. This included the proportion of the population that was male versus female, baseline age, baseline HAQ–Disability Index score, and patient weight. Stratification by disease severity (i.e., moderate or severe) was not explored by the sponsor.

Model Input: Treatment Effectiveness

The sponsor submitted separate NMAs informed from randomized controlled trials of relevant treatments for the two patient cohorts at 12-week (csDMARD-IR and bDMARD-IR) and 24-week time points (csDMARD-IR). The 12-week results were applied in the base-case analysis to inform the transition probabilities of all treatments according to ACR response (i.e., ACR20, ACR50, or ACR70) and nonresponse after the evaluation period (i.e., the initial three months). Patients who achieved the minimum ACR response were assumed to maintain the treatment effect (i.e., no improvement or deterioration in ACR response) and continue receiving treatment until experiencing a long-term discontinuation or death. To consider long-term discontinuation, a constant discontinuation rate was applied according to ACR response and assumed to be independent of treatment. The sponsor derived discontinuation probabilities using methods outlined in a technology assessment report commissioned by the National Institute for Health and Care Excellence (NICE).[10] The sponsor fitted parametric survival models to individual patient data using a generalized gamma distribution to estimate treatment discontinuation based on European League Against Rheumatism responses. Alternative parametric distributions were explored as part of sensitivity analyses by the sponsor.

Owing to a lack of data for subsequent treatment transition probabilities, the sponsor derived values using a weighted average of the efficacy from all initial treatments, excluding the previous treatment received by the patient, according to ACR response and nonresponder health states. The sponsor assumed that patients would continuously receive treatment and maintain the treatment effect until long-term discontinuation. Nonresponders and patients who discontinued on subsequent treatment received BSC; however, as patients previously failed to achieve a minimum response on this treatment, the sponsor assumed no clinical benefit would be received by the patients.

Model Input: Utilities

The sponsor measured patient quality of life using HAQ scores. A mean reduction in HAQ scores according to ACR response and nonresponse was calculated using the methodology outlined by Kielhorn et al. (2008)[11] in the sponsor's base case. As part of scenario analyses, HAQ scores according to ACR response were derived using the study by Soini et al. (2012).[12]

In the sponsor's base case, patient HAQ scores were mapped to HUI-3 values using a linear regression transformation.[13] The base-case HUI-3 values are shown in Table 9. An alternative regression approach from Soini et al. (2012)[12] was explored in scenario analyses, where the sponsor applied a nonlinear mixed model to map HAQ scores to values from the EQ-5D questionnaire. In addition, analyses from Chiou et al. (2005)[14] were used to estimate utility values directly from ACR response. While on treatment, HAQ gains were assumed to be maintained; when treatment is discontinued HAQ scores were assumed to worsen immediately and equal the initial HAQ gains while on treatment.

The sponsor base-case model included utility decrements due to SAEs, with the assumption that utility decrements for all SAEs were similar to those for serious infections. The sponsor calculated a utility decrement of –0.005 per event using published information.[15,16] An alternate utility decrement using Chiou et al. (2005)[14] was explored as part of scenario analyses.

Model Input: Adverse Events

The combined incidence of all reported SAEs was included in the sponsor's economic model based on an NMA previously conducted by CADTH on the relative benefits and harms of treatments used in moderate-to-severe RA patients who are intolerant to methotrexate.[4] This NMA was updated by the sponsor to include missing treatments (i.e., adalimumab 40 mg, tofacitinib 5/11 mg, baricitinib 2 mg, sarilumab 150/200 mg, tocilizumab SC, and upadacitinib) as part of the network. An overview of SAE probabilities is shown in Table 10.

Model Input: Health Care Resource Use and Costs

Upadacitinib acquisition costs were supplied by the sponsor. Drug acquisition costs for comparators were obtained from AbbVie Canada or the most recent price on the Ontario Drug Benefit Formulary.[17] Drug dosing schedules were aligned with Health Canada approved doses as per their respective product monographs. Weight-based dosing was calculated using a pooled mean baseline weight of 79.50 kg to align with patients from the SELECT clinical trials. All treatment costs were assumed to include wastage. Patients on BSC were assumed to incur the average costs of initial bDMARD and tsDMARD treatments until death or the end of the model time horizon.

As part of the sponsor's base case, drug administration costs were applied to IV and SC treatments, with the assumption that no costs would be incurred by patients receiving oral treatments. The sponsor assumed that the cost of a one-hour nursing visit[18] plus a 22.5% fringe benefit[19] ($44.17) would be applied to SC treatments and IV treatments. Costs were obtained from Tam et al. (2013),[20] a cost-utility analysis for metastatic pancreatic cancer patients, and inflated to 2019 Canadian dollars ($189.67).[21]

The estimated frequency of monitoring and follow-up care was based on the Canadian Rheumatology Association treatment guidelines and clinical expert opinion. Unit costs were obtained from the Ontario Schedule of Benefits for Physician/Laboratory Services[22,23] and the Ontario Case Costing Initiative analysis tool[15] for estimating facility costs. SAE costs were obtained from the Ontario Case Costing Initiative analysis tool and were based on the cost for serious infection ($15,631.43).[15]

Sponsor's Base Case

csDMARD-IR Population

In the base case, the sponsor reported that csDMARD monotherapy is the least costly treatment ($78,769) and provides the fewest QALYs (2.31) over a five-year time horizon. Based on a full sequential analysis, a csDMARD is the preferred option if a decision-maker's WTP is below $74,979 per QALY; infliximab 3 mg/kg + csDMARD is the preferred option if the WTP is between $74,979 and $80,897 per QALY; etanercept 50 mg + csDMARD is the preferred option if the WTP is between $80,897 and $107,659 per QALY; and upadacitinib + csDMARD is the preferred option if the WTP is more than $107,659 per QALY (Table 2). Other treatments were dominated (i.e., more costly and fewer QALYs than another treatment) or, in the case of upadacitinib monotherapy, extendedly dominated (i.e., more costly and fewer QALYs than a linear combination of two other strategies). A breakdown of the full results, including dominated strategies, is presented in Table 12.

bDMARD-IR Population

In the base case, the sponsor reported that csDMARD monotherapy costs the least ($82,984) and provides the fewest QALYs (2.24) over a five-year time horizon. Based on a

full sequential analysis, a csDMARD is the preferred option if a decision-maker's WTP is below $104,193 per QALY; upadacitinib + csDMARD is the preferred option if the WTP is between $104,193 and $303,516 per QALY; and tocilizumab 8 mg/kg is the preferred option if the WTP is more than $303,516 per QALY (Table 2). Other treatments were dominated or extendedly dominated. A breakdown of the full results, including dominated strategies, is presented in Table 13.

Table 2: Summary of Results of the Sponsor's Base Case

Treatment	Total costs, $	Total QALYs	Pairwise ICUR (UPA 15 mg + csDMARD vs. comparator), $/QALY	Sequential ICUR, $/QALY
csDMARD-IR				
csDMARD	78,769	2.31	83,360	-
IFX 3 mg/kg + csDMARD	86,225	2.41	92,006	74,979
ETN 50 mg + csDMARD	90,787	2.46	107,659	80,897
UPA 15 mg + csDMARD	95,096	2.50	-	107,659
bDMARD-IR				
csDMARD	82,984	2.24	104,193	-
UPA 15 mg + csDMARD	97,033	2.37	-	104,193
TCZi 8 mg/kg + csDMARD	106,835	2.41	303,516[a]	303,516

bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = responded inadequately or are intolerant to one or more bDMARDs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; ETN = etanercept; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; TCZi = IV tocilizumab; UPA = upadacitinib; vs. = versus.

Note: Only nondominated strategies are presented. Sequential ICUR = ICUR vs. previous treatment listed.

[a] Pairwise comparison of tocilizumab 8 mg/kg + csDMARD versus upadacitinib + csDMARD.

Source: Adapted from sponsor's pharmacoeconomic submission.[2]

Summary of Sponsor's Sensitivity Analyses

The sponsor conducted multiple scenario analyses, which focused on pairwise comparisons of upadacitinib + csDMARD with etanercept 50 mg + csDMARD in the csDMARD-IR population and tofacitinib 5 mg + csDMARD in the bDMARD-IR population. The scenarios explored included discount rate, time horizon, efficacy end point (six months), BSC after failure of initial treatment, distribution for long-term discontinuation, utility type, utility decrement, drug wastage, administration costs, csDMARD as BSC, and a societal perspective. The ICUR ranged from $61,392 to $354,004 per QALY for the csDMARD-IR population and $239 to $71,881 per QALY in the bDMARD population. Additionally, upadacitinib + csDMARD dominates tofacitinib 5 mg + csDMARD in the following scenarios: three-year time horizon, societal perspective, Weibull distribution for long-term discontinuation, utility decrement by ACR response, and the exclusion of drug wastage.

Limitations of Sponsor's Submission

- **Uncertainty associated with the comparative efficacy estimates**: The CADTH clinical review found that although the NMA for the csDMARD-IR population indicated that patients receiving upadacitinib may have a greater probability of achieving an ACR20 response than those receiving other available bDMARDs and tsDMARDs, there are some minor limitations that leave the magnitude of any potential benefit uncertain. Further, the CADTH clinical review highlighted high statistical uncertainty with the NMA for the bDMARD-IR population due to a limited number of trials being included in the network. The cost-effectiveness results should be viewed within the context of these findings.
- **Uncertainty associated with derivation of health state utilities**: The sponsor applied a linear transformation regression cross-sectional model as part of its base case; however, it was noted by Boggs et al. that the relationship between HAQ and HUI-3 was likely nonlinear, and the use of basic linear regression is limited. The basic linear regression was also associated with a low model fit (adjusted $R^2 = 0.49$), indicating large variation with the estimates, and was improved when incorporating nonlinear coefficients, which were not incorporated in the base case by the sponsor. The CADTH review of baricitinib and the health technology assessment conducted by NICE for RA treatments also concluded that mixture models that incorporated both pain and HAQ to derive EQ-5D utilities were more accurate than linear models and that an improvement in fit is typically observed at very poor and very good health states when using the methodologies outlined by Hernandez et al.[5,7,24,25] Because of the uncertainty associated with using a linear regression to map utilities, it was considered most appropriate to apply the nonlinear regression equation from the study by Soini et al. (2012)[12] as part of CADTH's base case, since this represents the best available data included in the sponsor's economic model owing to an improved model fit. However, a mixture model based on the methodology outline by Hernandez et al. (2013) would have been preferred.[24]
- **EQ-5D data from trials not used**: Despite the availability of EQ-5D data from the SELECT clinical trials, the sponsor derived health state utilities by mapping HAQ scores. According to CADTH economic guidelines, the use of indirect generic classification systems (i.e., EQ-5D) is preferred in the base case and utility mapping (i.e., HAQ to HUI-3 or EQ-5D) to be explored as part of sensitivity analyses.[26] Using utility mapping adds unnecessary variation and uncertainty into the economic model. EQ-5D–based utility values stratified according to ACR response were not included in the economic submission.
- **Cost-effectiveness in moderate or severe disease not explored**: The sponsor's analyses were not stratified according to moderate or severe disease. It is therefore uncertain to what impact upadacitinib has on improving patient disease activity in these subpopulations, which may require distinct treatment sequencing. Multiple public drug programs (e.g., Alberta, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Non-Insured Health Benefits) have restricted treatment access for some or all bDMARDs and tsDMARDs to severely active RA patients only.[27-32] Therefore, presenting results for the total moderate-to-severe RA patient population may limit a decision-maker's ability to assess upadacitinib's optimal place in therapy for reimbursement. Previous assessments by health technology assessment agencies reported results stratified based on moderate or severe RA for similar treatments (baricitinib and tofacitinib) in both subpopulations.[5,33-36] Both NICE and the Scottish Medicine Consortium provided recommendations for restricted use in severe RA patients only. Because of the structural limitations of the model, CADTH was unable to explore the cost-effectiveness of upadacitinib for these subpopulations.

- **Limited subsequent treatments were considered**: The clinical expert consulted by CADTH highlighted that the sponsor's treatment sequencing was not likely to be reflective of clinical practice, as the majority of patients would receive more than two bDMARD or tsDMARD treatments before receiving BSC. According to the Canadian RA guidelines[37] and clinical expert feedback, RA patients failing subsequent treatments would continue to receive additional bDMARD or tsDMARD treatments that use a different mechanism of action. Although using the same follow-up sequence for all comparators minimizes confounders when evaluating upadacitinib as initial treatment, treatment sequences are highly individualized, and this variability was not captured in the sponsor's analyses to identify the optimal positioning for upadacitinib. CADTH acknowledges that data to inform subsequent treatments are likely limited and using a simplifying assumption for subsequent treatment may be reasonable. However, because of the structural limitations of the economic model, CADTH could not explore the impact of additional treatment sequences before receiving BSC, which would better reflect clinical practice.
- **Application of subsequent treatments**: The application of a weighted efficacy for subsequent treatments that excludes the prior treatment received also adds further uncertainty to the assessment of upadacitinib, as efficacy may be over- or underestimated depending on the initial treatment received. Therefore, in CADTH's base case, equal efficacy and costs were applied to subsequent treatment. Additionally, the subsequent treatment efficacy for upadacitinib monotherapy and upadacitinib + csDMARD was excluded from comparators in the csDMARD-IR economic model, which underestimates the benefit gain associated with subsequent treatment and was corrected in CADTH reanalyses.
- **Inappropriate costs of BSC**: In the sponsor's base case, BSC was assumed to be a prior therapy that achieved the best treatment effect. However, the clinical expert consulted by CADTH indicated that patients would not receive a treatment that had previously been used owing to payer restrictions and would instead be given a csDMARD and/or glucocorticoids once available treatment options had been exhausted. Additionally, other reviews by NICE and the Institute for Clinical and Economic Review, and the CADTH review of baricitinib, highlighted that BSC would be a combination of csDMARDs.[5-7] Since the sponsor assumed patients receiving BSC would incur the average costs of bDMARD and tsDMARD treatments, this would substantially overestimate the treatment costs associated with BSC and favour treatments that delay the transition to BSC. In CADTH's base case, the cost of csDMARDs was applied for both the csDMARD-IR and bDMARD-IR populations and the costs of bDMARDs and tsDMARDs were applied in scenario analyses.
- **Applicability of administration costs**: The sponsor included administration costs for SC and IV treatments; however, as indicated in previous tsDMARD submissions to CADTH (i.e., tofacitinib and baricitinib), and in line with feedback from the clinical expert consulted by CADTH, administration costs would likely not be incurred by the public payer.[5,38] The stated SC treatments would be self-administered by the patient, and no administration costs would be expected for these treatments. Additionally, the clinical expert highlighted that infusion costs are typically incurred by the manufacturers. However, the CADTH reviews of tofacitinib and baricitinib highlighted that some patients may receive infusions at publicly funded outpatient clinics. Administration costs for SC and IV treatments were removed in CADTH's base-case reanalyses.
- **Short model time horizon**: RA is a chronic inflammatory disease, and the five-year time horizon used by the sponsor does not capture the total accrued costs and QALYs experienced by patients. Although the model allowed a time horizon of up to 20 years,

CADTH did not explore the long-term cost-effectiveness of upadacitinib, as a constant treatment effect was assumed, and treatment waning was not incorporated in the economic model. The CADTH base case used a five-year time horizon; however, a lifetime time horizon is preferred.

- **RA-related mortality not included**: The clinical expert consulted by CADTH indicated that RA patients have an elevated mortality risk. The study by Widdifield et al. (2018)[39] supported this assessment, as Canadian RA patients were associated with a higher mortality rate than the general population (overall mortality rate ratio: 1.40). Although mortality is likely unaffected by treatment, applying a lower mortality biases results in favour of more efficacious treatments, including upadacitinib, as patients achieving a minimal ACR response will only discontinue treatment owing to long-term discontinuation and death. As part of CADTH base-case reanalyses, the mortality rate ratio from Widdifield et al. (2018) was applied to general population mortality rates and converted to probabilities, and the removal of RA-specific mortality was explored in scenario analyses.
- Additionally, the sponsor used mortality data from 2014 to 2016, when results for 2015 to 2017 were available. The mortality data were corrected as part of CADTH reanalyses to reflect the more up-to-date values.

CADTH Common Drug Review Reanalyses

CADTH reanalyses included the following changes to the sponsor's base case:

1. Made a correction to resource use for laboratory blood tests based on sponsor's report (see Table 8), revised drug costs for baricitinib and tofacitinib, updated mortality data, included upadacitinib as subsequent treatment in the csDMARD-IR analysis.
2. Incorporated RA patient mortality using the study by Widdifield et al. (2018).
3. Applied the costs of csDMARD for BSC.
4. Removed administration costs associated with SC and IV treatments.
5. Assumed equal efficacy and costs for subsequent treatments.
6. Applied baseline HAQ to nonresponders and patients discontinuing treatment (see Table 11).
7. Used nonlinear mapping equation of HAQ scores to EQ-5D utilities.
8. **CADTH base case (1+2+3+4+5+6+7).**

CADTH assessed various parameters, and the following key scenario analysis results are presented on the CADTH base case:

8a. initial HAQ scores of 0.5, 1.0, 2.0, and 2.5

8b. HAQ score reduction according to ACR response from Soini et al. (2012), Carlson et al. (2015), and Schlueter et al. (2019)

8c. equal discontinuation rate of 8.3% per cycle obtained from Carlson et al. (2015)

8d. BSC costs reflected by bDMARD and tsDMARD

8e. use of a societal perspective (based on sponsor's inputs)

8f. removal of RA-specific mortality

8g. application of a 20-year time horizon.

CADTH's base-case results are presented in Table 3. Additional analyses and results are presented in Table 14 to Table 19.

csDMARD-IR Population

In CADTH's base case, csDMARD monotherapy costs the least ($35,296) and provides the fewest QALYs (2.77) over a five-year time horizon. According to a full sequential analysis, a csDMARD is the preferred option if a decision-maker's WTP is below $127,425 per QALY; etanercept 50 mg + csDMARD is the preferred option if the WTP is between $127,425 and $323,344 per QALY; and upadacitinib + csDMARD is the preferred option if the WTP is more than $323,344 per QALY (Table 3). At a WTP of $50,000 per QALY, 0.5% of simulations resulted in upadacitinib + csDMARD being cost-effective. Upadacitinib monotherapy remains extendedly dominated (i.e., more costly and fewer QALYs than a linear combination of two other strategies).

bDMARD-IR Population

In CADTH's base case, csDMARD monotherapy costs the least ($31,136) and provides the fewest QALYs (2.68) over a five-year time horizon. According to a full sequential analysis, a csDMARD is the preferred option if a decision-maker's WTP is below $194,423 per QALY; upadacitinib + csDMARD is the preferred option if the WTP is between $194,423 and $231,785 per QALY; and tocilizumab 8 mg/kg + csDMARD is the preferred option if the WTP is more than $231,785 per QALY (Table 3). At a WTP of $50,000 per QALY, 3.5% of simulations resulted in upadacitinib + csDMARD being cost-effective.

Table 3: CADTH Base-Case Results

Scenario	Treatment	Total costs, $	Total QALYs	Sequential ICUR, $/QALY
CADTH base case (1+2+3+4+5+6+7)	**csDMARD-IR**			
	csDMARD	35,296	2.77	-
	ETN 50 mg + csDMARD	56,844	2.94	127,425
	UPA 15 mg + csDMARD	69,034	2.98	323,344
	bDMARD-IR			
	csDMARD	31,136	2.68	-
	UPA 15 mg + csDMARD	58,650	2.83	194,423
	TCZi 8 mg/kg + csDMARD	65,908	2.86	231,785

bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; ETN = etanercept; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZi = IV tocilizumab; UPA = upadacitinib.

Note: Only nondominated strategies are presented. Sequential ICUR = ICUR versus previous treatment listed.

Exploratory scenario analyses were conducted using the CADTH base case to investigate the impact of initial HAQ scores, HAQ score reduction by ACR response, long-term discontinuation rate, removal of RA-specific mortality, use of a societal perspective, extension of the time horizon (20 years), and bDMARD and tsDMARD costs for BSC (Table 17). A scenario where csDMARD treatment was removed for both the csDMARD-IR and bDMARD-IR populations was explored to assess the cost-effectiveness impact when upadacitinib is only compared to bDMARDs and tsDMARDs (Table 20).

csDMARD-IR Population

In these scenarios, the ICURs for upadacitinib + csDMARD ranged from $201,692 (initial HAQ = 2.5) to $778,700 (initial HAQ = 0.5) per QALY versus etanercept 50 mg + csDMARD

(see Table 17). ICURs were increased for upadacitinib when baseline HAQ scores were below the mean reported value from the SELECT clinical trials (1.52), HAQ score reductions according to ACR response from Soini et al. (2012) and Carlson et al. (2015) were applied, and long-term discontinuation was adjusted. Conversely, ICURs for upadacitinib improved when baseline HAQ scores were greater than 1.52, RA-specific mortality was removed, the time horizon was extended to 20 years, a societal perspective was adopted, and bDMARD/tsDMARD treatment costs for BSC were included.

bDMARD-IR Population

In these scenarios, the ICURs for upadacitinib + csDMARD ranged from $116,257 (bDMARD/tsDMARD treatment costs for BSC) to $434,206 (initial HAQ = 0.5) per QALY versus csDMARD monotherapy (see Table 17). ICURs were increased for upadacitinib when baseline HAQ scores were below the mean reported value from the SELECT clinical trials (1.52), HAQ score reductions according to ACR response from Soini et al. (2012) and Carlson et al. (2015) were applied, long-term discontinuation was adjusted, and RA-specific mortality was removed. Conversely, ICURs for upadacitinib improved when baseline HAQ scores were greater than 1.52, the time horizon was extended to 20 years, a societal perspective was adopted, and bDMARD/tsDMARD treatment costs for BSC were included.

Price Reduction Analyses

Price reduction analyses were conducted using both the sponsor and CADTH base case (Table 18 and Table 19). When using the CADTH base case, if a decision-maker's WTP is $50,000 per QALY, upadacitinib would require a price reduction of 50% to 60% (csDMARD-IR population) or 60% to 70% (bDMARD-IR population) for upadacitinib + csDMARD to be considered cost-effective.

Price reduction analyses were also explored when csDMARD was excluded from both the csDMARD-IR and bDMARD-IR populations, as this treatment is unlikely to be used in this line of therapy (Table 21 and Table 22). When using the CADTH base case, if a decision-maker's WTP is $50,000 per QALY, upadacitinib would require a price reduction of 5% (bDMARD-IR population) or 30% to 35% (csDMARD-IR population) for upadacitinib + csDMARD to be considered cost-effective. However, as other tsDMARDs are currently in active price negotiations (baricitinib) or recently completed price negotiations (tofacitinib) with the pan-Canadian Pharmaceutical Alliance, the actual cost of these treatments is unknown. If negotiations have led to a lower price for the comparator treatments, the price reductions required for upadacitinib to be considered cost-effective at a WTP of $50,000 per QALY may be underestimated.

Issues for Consideration

- **Previous reviews of JAK inhibitors**: CADTH reviewed tofacitinib and baricitinib for patients with moderate-to-severe RA in 2015 and 2019, respectively. The CADTH Canadian Drug Expert Committee (CDEC) recommended that tofacitinib be reimbursed, with the condition that the "drug plan cost for tofacitinib not to exceed the drug plan costs for the biologic DMARDs reimbursed."[40] More recently, CADTH reviewed baricitinib and recommended that the "drug plan cost of treatment with baricitinib should result in cost-savings compared with the drug plan cost of treatment with the least costly alternative bDMARD."[41] Based on the CDEC price reduction recommendations, it is unknown if the prices of JAK inhibitors used in the economic model are reflective of actual prices.

- **Included dosing**: The SELECT clinical trials (EARLY, NEXT, MONOTHERAPY, BEYOND) included a 30 mg dose for upadacitinib, which is not currently available in Canada and was not explored in the sponsor's submission. It is therefore uncertain what the cost-effectiveness of upadacitinib would be if the 30 mg dose were to become available. Additionally, the sponsor included the 4 mg tablet of baricitinib in the economic model, which is not currently approved in Canada.

Patient Input

Input was received by two patient groups: A joint submission from the Arthritis Society and the Canadian Arthritis Patient Alliance and a second submission from the Arthritis Consumer Experts. The patient groups highlighted that RA impacts their day-to-day lives, such as having difficulty completing daily tasks owing to joint stiffness, pain, brain fog, and overall fatigue. The sponsor included HAQ and ACR scales in the economic model to reflect these factors in the analyses.

As a result of the negative consequences of the disease on patients' ability to function, RA impacts both employment and financial status. Many patients were no longer able to work, accepted a demotion, received Canadian Pension Plan disability, or withdrew from postgraduate studies. The sponsor presented an analysis from the societal perspective, which included productivity and leisure time loss for both csDMARD-IR and bDMARD-IR patient populations.

Conclusions

The CADTH reanalyses aligned with the sponsor's base-case analyses, indicating that upadacitinib as monotherapy or in combination with a csDMARD is not a cost-effective treatment at conventionally accepted WTP thresholds. In the csDMARD-IR population, upadacitinib + csDMARD is the preferred option if a decision-maker's WTP is more than $323,344 per QALY; at a lower WTP, either csDMARD monotherapy or etanercept 50 mg + csDMARD would be the optimal treatment. In the bDMARD-IR population, upadacitinib + csDMARD is the preferred treatment if a decision-maker's WTP is between $194,423 and 231,785 per QALY; at a lower WTP, csDMARD monotherapy is the optimal treatment, while at a higher WTP, tocilizumab 8 mg/kg + csDMARD is the optimal therapy. Scenario analyses that excluded csDMARD as a comparator were also undertaken. Upadacitinib was not cost-effective at a WTP of $50,000 per QALY in these analyses.

Price reductions can improve the cost-efficiency of upadacitinib + csDMARD in patients with moderate-to-severe RA:

- csDMARD-IR: If a decision-maker's WTP threshold is $100,000 and $50,000 per QALY, a price reduction of approximately 30% and 50% to 60%, respectively, is required for upadacitinib + csDMARD to be considered cost-effective. If csDMARD treatment is excluded from analyses, a 30% to 35% price reduction is required for upadacitinib monotherapy and upadacitinib + csDMARD to be considered cost-effective at a WTP of $50,000 per QALY compared to infliximab 3 mg/kg + csDMARD and upadacitinib monotherapy, respectively.

- bDMARD-IR: If a decision-maker's WTP threshold is $100,000 and $50,000 per QALY, a price reduction of approximately 40% and 60% to 70%, respectively, is required for upadacitinib + csDMARD to be considered cost-effective. If csDMARD treatment is excluded from analyses, a price reduction of approximately 5% is required for upadacitinib + csDMARD to be considered cost-effective at a WTP of $50,000 per QALY.

However, several limitations were identified that could not be addressed in the submitted model, most notably the inability to explore the cost-effectiveness for moderate or severe RA patients and the need for long-term extension of the time horizon. In line with the findings of the economic evaluation, the results of the sponsor's NMA indicated that upadacitinib was more efficacious than other available RA treatments in achieving a minimum ACR response.

Appendix 1: Cost Comparison

The comparators presented in the Table 4 have been deemed 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 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 4: CADTH Cost Comparison Table of DMARDs

Drug/comparator	Strength	Dosage form	Price, $	Recommended dosage	Average annual drug cost, $
Upadacitinib (Rinvoq)	**15 mg**	**Tablet**	**48.6843[a]**	**15 mg daily**	**17,770**
tsDMARDs					
Baricitinib (Olumiant)	2 mg	Tablet	47.9176	2 mg daily	17,490
Tofacitinib (Xeljanz)	5 mg	Tablet	23.9589	5 mg twice daily	17,490
	11 mg	ER tablet	47.9178[b]	11 mg daily	
bDMARDs, anti-TNF					
Adalimumab SC (Humira)	40 mg/0.8 mL	Pre-filled syringe or pen	769.9700	40 mg every 2 weeks	20,074
Certolizumab pegol (Cimzia)	200 mg/mL	Pre-filled syringe or auto-injector	664.5100[c]	400 mg at weeks 0, 2, and 4, then 200 mg every 2 weeks	Year 1: 19,318 Thereafter: 17,325
Etanercept (Enbrel)	25 mg	Vial	202.9300	50 mg weekly or two 25 mg doses on same day every week or every 3 or 4 days	21,163
	50 mg/mL	Pre-filled syringe or auto-injector	405.9850		21,169
Etanercept (Brenzys)	50 mg/mL	Pre-filled syringe or auto-injector	254.0000	50 mg weekly	13,244
Etanercept (Erelzi)	25 mg/0.5 mL 50 mg/mL	Pre-filled syringe or auto-injector	127.5000 255.0000	50 mg weekly or two 25 mg doses on same day every week or every 3 or 4 days	13,296
Golimumab SC (Simponi)	50 mg/0.5 mL 100 mg/mL	Pre-filled syringe or auto-injector	1,555.5000[c]	50 mg monthly	18,666
Golimumab IV (Simponi)	50 mg/4.0 mL	Vial	879.5000[c]	2 mg/kg at weeks 0 and 4, then every 8 weeks thereafter	Year 1: 18,470 Thereafter: 17,197
Infliximab (Remicade)	100 mg	Vial	977.0000[c]	3 mg/kg at weeks 0, 2, and 6, then every 8 weeks thereafter	Year 1: 23,448 Thereafter: 19,104 Max.: 101,887

Drug/comparator	Strength	Dosage form	Price, $	Recommended dosage	Average annual drug cost, $
Infliximab (Inflectra)	100 mg	Vial	525.0000	Depending on clinical response, dose can be increased to 10 mg/kg and/or up to every 4 weeks	Year 1: 12,600 Thereafter: 10,266 Max.: 54,750
Infliximab (Renflexis)	100 mg	Vial	493.0000		Year 1: 11,832 Thereafter: 9,640 Max: 51,413
bDMARDs, non-TNF					
Abatacept SC (Orencia)	125 mg/mL	Pre-filled syringe	373.7900[c]	125 mg weekly	19,490
Abatacept IV (Orencia)	250 mg/15 mL	Vial	500.3400[c]	< 60 kg: 500 mg 60 to 100 kg: 750 mg > 100 kg: 1,000 mg 500 to 1,000 mg at weeks 0, 2, and 4, then every 4 weeks	Year 1: 22,568 Thereafter: 19,567
Rituximab (Rituxan)	10 mg/mL	Vial	48.2305[c]	A course consists of 1,000 mg infusions at weeks 0 and 2; reassess for retreatment at week 26, no sooner than 16 weeks after previous	19,292, assuming 2 courses Per course: 9,646
Sarilumab (Kevzara)	150 mg/1.14 mL 200 mg/1.14 mL	Pre-filled syringe/pen	721.0000[b]	200 mg SC every 2 weeks	18,250
Tocilizumab SC (Actemra)	162 mg/0.9 mL	Pre-filled syringe	358.9050[b]	< 100 kg: 162 mg SC every 2 weeks, increasing to weekly based on clinical response; ≥ 100 kg: 162 mg SC weekly	9,357 to 18,714
Tocilizumab IV (Actemra)	80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	Vial	182.8000[c] 457.0000[c] 914.0000[c]	4 mg/kg every 4 weeks, then increase to 8 mg/kg based on clinical response	9,532 to 19,063
csDMARDs					
Hydroxychloroquine (Generic)	200 mg	Tablet	0.1576	200 mg to 400 mg daily	58 to 115
Leflunomide (Generic)	10 mg 20 mg 100 mg	Tablet	2.6433 2.6433 NR	10 mg to 20 mg daily	965
Methotrexate (Generic)	2.5 mg	Tablet	0.6325	7.5 mg weekly; 2.5 mg at 12 hour intervals	99
Methotrexate IV (Generic)	20 mg/2 mL 50 mg/2 mL	Vial	12.5000 8.9200	20 mg total weekly dose	652
Methotrexate SC (Metoject)	7.5 mg/0.75 mL 15 mg/0.3 mL 17.5 mg/0.35 mL 20 mg/0.4 mL 22.5 mg/0.45 mL 25 mg/0.5 mL	Pre-filled syringe	28.0800[c] 32.7600 32.0000 35.0000 35.0000 39.0000	7.5 to 25 mg per week	1,464 to 2,034

Drug/comparator	Strength	Dosage form	Price, $	Recommended dosage	Average annual drug cost, $
Sulfasalazine (Salazopyrin)	500 mg	ER tablet	0.2816	Week 1: 500 mg daily Week 2: 500 mg twice daily Week 3: 500 mg three times daily Week 4+: 2 g to 3 g daily	Year 1: 399 to 593 Thereafter: 411 to 617

DMARD = disease-modifying antirheumatic drug; ER = extended release; Max. = maximum; NR = not reported; SC = subcutaneous; TNF = tumour necrosis factor.

Note: All prices are from the Ontario Drug Benefit Formulary (August 2019)[17] unless otherwise indicated and do not include dispensing fees. Costs are based on 365 days per year, using the maintenance dosage where applicable. All weight-based doses assume an average patient weight of 75 kg and wastage of excess medication in vials.

[a] Sponsor-submitted price.[2]

[b] Alberta Formulary (accessed August 2019).[42]

[c] Saskatchewan Formulary (accessed August 2019).[43]

Appendix 2: Additional Information

Table 5: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?		X	
Comments	Additional request was made to sponsor to provide integrated results for the csDMARD-IR and bDMARD-IR populations; the results were received by CADTH.		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; csDMARD-IR = responded inadequately or are intolerant to one or more conventional synthetic disease-modifying antirheumatic drugs.

Table 6: Author Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☐ 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

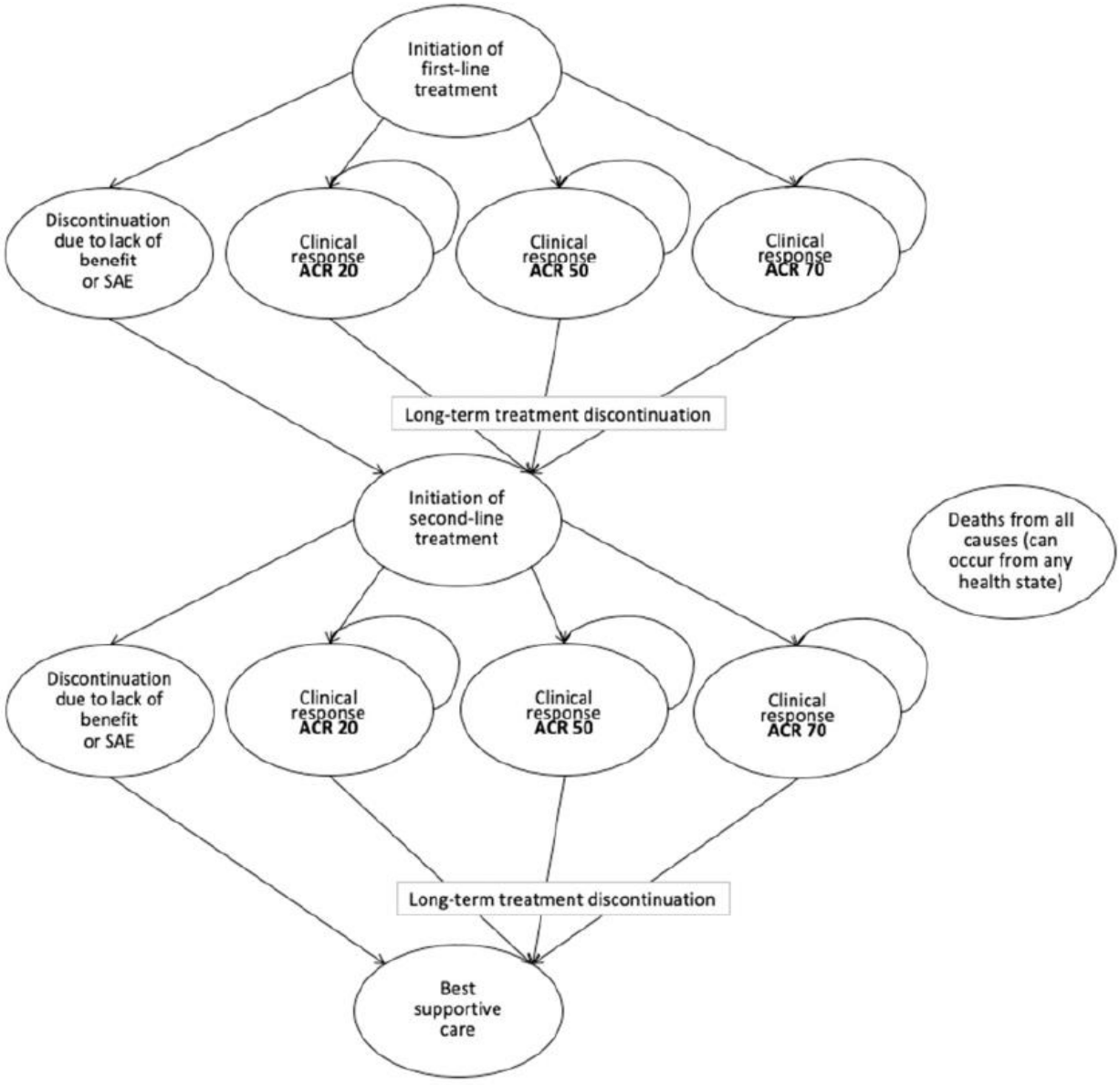
☐ Other (please specify)

	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: Reviewer Worksheets

Model Structure

Figure 1: Sponsor's Markov Model Structure



ACR = American College of Rheumatology; SAE = serious adverse event.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 7: Included Comparators According to Patient Population

	12 weeks csDMARD-IR	24 weeks csDMARD-IR	12 weeks bDMARD-IR
bDMARD			
Abatacept 10 mg/kg + csDMARD	Included	Included	Included
Abatacept 125 mg + csDMARD	Included	Included	Excluded
Adalimumab 40 mg	Included	Included	Excluded
Adalimumab 40 mg + csDMARD	Included	Included	Excluded
Certolizumab pegol 200 mg + csDMARD	Included	Included	Included
Etanercept 50 mg	Included	Included	Excluded
Etanercept 50 mg + csDMARD	Included	Included	Excluded
Golimumab 50 mg + csDMARD	Included	Included	Included
Infliximab 3 mg/kg + csDMARD	Included	Included	Excluded
Rituximab 2,000 mg + csDMARD	Excluded	Included	Included
Sarilumab 150 mg + csDMARD	Excluded	Included	Included
Sarilumab 200 mg	Included	Included	Excluded
Sarilumab 200 mg + csDMARD	Excluded	Included	Included
Tocilizumab 8 mg/kg	Included	Included	Excluded
Tocilizumab 8 mg/kg + csDMARD	Included	Included	Included
Tocilizumab 162 mg	Included	Included	Excluded
Tocilizumab 162 mg + csDMARD	Excluded	Included	Excluded
tsDMARD			
Baricitinib 2 mg + csDMARD	Included	Included	Included
Baricitinib 4 mg + csDMARD	Excluded	Excluded	Included
Tofacitinib 5 mg	Included	Included	Excluded
Tofacitinib 5 mg + csDMARD	Included	Included	Included
Tofacitinib 11 mg + csDMARD	Excluded	Excluded	Included
csDMARD			
Methotrexate 2.5 mg Leflunomide 20 mg Sulfasalazine 500 mg Hydroxychloroquine 200 mg	Included	Included	Included

bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = responded inadequately or are intolerant to one or more bDMARDs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Note: The comparator csDMARD consisted of treatment with either methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine.

Source: Adapted from the sponsor's pharmacoeconomic submission.[2]

Summary of Sponsor Data Sources

Table 8: Model Data Sources

Data input	Description of data source	Comment
Efficacy and natural history	The sponsor submitted an unpublished NMA using ACR response as the main clinical outcome for the csDMARD-IR and bDMARD-IR patient populations. The NMA reported results for ACR20/50/70 responders and nonresponders at 12 weeks for initial treatment in the base case. Efficacy results at 24 weeks for csDMARD-IR patients were also available.	Source acceptable. However, the bDMARD-IR NMA was associated with uncertainty due to the sparse network and limited number of clinical trials. See CADTH Clinical Review Report for additional information.
	Long-term discontinuation was derived using parametric survival distributions (generalized gamma) based on a technology assessment commissioned by NICE.[10] Because of the paucity of data for long-term discontinuation according to ACR response, the sponsor used EULAR response in the analyses.	Uncertain. Although CADTH considered the methodology stated by the sponsor to be reasonable, the assumption of applying EULAR responses introduces additional variation into the analyses. To assess the impact of long-term discontinuation, CADTH applied equal discontinuation rates for nonresponders and all ACR responses from Carlson et al. (2015)[44] in scenario analyses.
Utilities	The mean reduction in HAQ score according to ACR response was obtained from Kielhorn et al. (2008).[11]	Uncertain. The sponsor applied HAQ score reductions from the published literature for both csDMARD-IR and bDMARD-IR populations. However, according to the SELECT-BEYOND trial data, bDMARD-IR patients appeared to have a lower reduction in HAQ at week 12 than csDMARD-IR patients. As HAQ scores according to ACR response from the SELECT clinical trials were not provided by the sponsor, CADTH was unable to determine the impact of HAQ reduction between the populations. Additionally, the sponsor applied HAQ score reductions from the published literature, which used trial data with assessments at 24 weeks, and applied these values directly in the model. Although the difference in reduction of HAQ between 12 weeks and 24 weeks is minimal, the impact on cost-effectiveness is uncertain.
	Utilities were mapped using a linear transformation model to HUI-3 values.	Uncertain. See Limitations of Sponsor's Submission. Alternative utility mapping methods (linear and nonlinear) were explored in sensitivity analyses using HAQ scores obtained from Soini et al. (2012)[12] and Chiou et al. (2005).[14]
	Utility decrements due to SAEs were derived using the utility decrement for serious infections obtained from Oppong et al. (2013)[16] and the total duration using the OCCI database.[15]	Source acceptable. Alternative SAE utility decrements were explored in sensitivity analyses using the value reported by Chiou et al. (2005).[14]
AEs	The sponsor included SAEs in the economic model based on the NMA conducted in the CADTH Health Technology Assessment for drugs used to manage RA. Since upadacitinib and other comparators (i.e., SAR, TCZ, ADA 40 mg, TOF 5/11 mg, BAR 2 mg) were not included	Uncertain. The methodology used to estimate SAEs was unclear and the data were not provided by the sponsor. However, CADTH adjusted the SAE probabilities to equal upadacitinib, and the impact on results was minimal.

Data input	Description of data source	Comment
	as part of the analyses, the incidence of SAEs was estimated using an NMA based on the comparison with placebo.	
Resource use and costs		
Drug	Dosing schedules were based on Health Canada approved doses in treatment product monographs. For weight-based dosing, the sponsor applied a mean baseline weight of 79.50 kg according to patient characteristics in the SELECT clinical trials (MONOTHERAPY, COMPARE, NEXT). The sponsor included drug wastage for both IV and SC treatments. The upadacitinib cost was based on the sponsor's submitted price, and comparator drug acquisition costs were obtained from the ODB Formulary.[17] Biosimilar costs were applied to etanercept and infliximab. Drug costs for csDMARDs were assumed to equal the cost of methotrexate.	Acceptable. Reasonable. However, the clinical expert consulted by CADTH highlighted that patients in the trial were older and had a greater mean weight than patients typically seen in routine practice. Acceptable. Reasonable. The cost of baricitinib 2 mg tablets was incorrectly assumed to be equivalent to upadacitinib 15 mg tablets. The price of baricitinib was corrected in CADTH's reanalyses using the submitted price of $47.92 per 2 mg tablet provided in the CADTH review of baricitinib.[5] Additionally, the price of tofacitinib was incorrectly input in the economic model and was subsequently corrected.
Administration	Patients receiving an SC treatment were assumed to receive a one-hour nursing visit. IV administration costs were obtained from Tam et al. (2013),[20] which studied chemotherapy administration costs in pancreatic cancer patients.	Inappropriate. See Limitations of Sponsor's Submission.
SAEs	The sponsor obtained hospitalization costs from the OCCI database for serious infections and applied these costs for any SAE.	Inappropriate. The clinical expert consulted by CADTH indicated that although serious infections may be most common, these are not representative of all SAEs with a substantial clinical and economic impact (i.e., major cardiac adverse events and thrombosis).
Medical services	The sponsor only included costs associated with monitoring and follow-up.	Uncertain. The sponsor's model underestimates direct medical resource use and costs, including cardiologist visits, emergency room visits, and surgeries as reported by Lathia et al. (2017).[45] In addition, the clinical expert consulted by CADTH indicated that the majority of patients would receive a vaccine for shingles, as this commonly occurs when on bDMARD or tsDMARD treatment. The sponsor's facility fees were overestimated when compared to the OHIP Schedule of Facility Fees,[46] which was the recommended data source according to the CADTH Guidance Document for Costing of Health Care Resources.[47]

Data input	Description of data source	Comment
		There were discrepancies in laboratory service use as the inputted economic model values were two times greater than what was stated in the report. The economic model was corrected in CADTH's base case to align with the sponsor's report.

ACR = American College of Rheumatology; ADA = adalimumab; AE = adverse event; BAR = baricitinib; bDMARD = biologic disease-modifying antirheumatic drug; bDMARD-IR = responded inadequately or are intolerant to one or more bDMARDs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; EULAR = European League Against Rheumatism; HAQ = Health Assessment Questionnaire; HUI-3 = Health Utility Index 3; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; OHIP = Ontario Health Insurance Plan; RA = rheumatoid arthritis; SAE = serious adverse event; SAR = sarilumab; SC = subcutaneous; TCZ = tocilizumab; TOF = tofacitinib; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Health State Utilities

Table 9: Estimated Health Utility Index 3 Values According to the ACR Response Criteria

Health state	Estimate	Data sources and notes
Nonresponder	0.401	Kielhorn et al. (2008) and linear model
ACR20	0.499	
ACR50	0.611	
ACR70	0.684	

ACR = American College of Rheumatology.

Source: Adapted from sponsor's pharmacoeconomic submission.[2]

Adverse Events

Table 10: Incidence of Serious Adverse Events in the Sponsor's Economic Model

	Estimate, %	Source
bDMARD		
Abatacept 10 mg/kg + csDMARD	0.99	CADTH NMA (2018)
Abatacept 125 mg + csDMARD	2.53	CADTH NMA (2018)
Adalimumab 40 mg	3.14	Assumed same as adalimumab 40 mg + csDMARD
Adalimumab 40 mg + csDMARD	3.14	CADTH NMA (2018)
Certolizumab pegol 200 mg + csDMARD	3.78	CADTH NMA (2018)
Etanercept 50 mg	3.20	CADTH NMA (2018)
Etanercept 50 mg + csDMARD	3.61	CADTH NMA (2018)
Golimumab 50 mg + csDMARD	6.11	CADTH NMA (2018)
Infliximab 3 mg/kg + csDMARD	1.80	CADTH NMA (2018)
Rituximab 200 mg + csDMARD	3.26	CADTH NMA (2018)
Sarilumab 150 mg + csDMARD	6.13	Updated CADTH NMA
Sarilumab 200 mg	6.13	Updated CADTH NMA
Sarilumab 200 mg + csDMARD	6.13	Updated CADTH NMA
Tocilizumab 8 mg/kg	4.80	CADTH NMA (2018)
Tocilizumab 8 mg/kg + csDMARD	7.07	CADTH NMA (2018)
Tocilizumab 162 mg	3.03	Updated CADTH NMA

	Estimate, %	Source
Tocilizumab 162 mg + csDMARD	3.03	Updated CADTH NMA
Subsequent bDMARD	4.11	CADTH NMA (2018)
tsDMARD		
Baricitinib 2 mg + csDMARD	1.42	CADTH NMA (2018)
Baricitinib 4 mg + csDMARD	1.42	Assumed same as baricitinib 2 mg + csDMARD
Tofacitinib 5 mg	6.34	Assumed same as tofacitinib 5 mg + csDMARD
Tofacitinib 5 mg + csDMARD	6.34	CADTH NMA (2018)
Tofacitinib 11 mg + csDMARD	6.34	Assumed same as tofacitinib 5 mg + csDMARD
Upadacitinib 15 mg	3.72	Updated CADTH NMA
Upadacitinib 15 mg + csDMARD	3.72	Updated CADTH NMA
csDMARD		
Methotrexate 2.5 mg, leflunomide 20 mg, sulfasalazine 500 mg, hydroxychloroquine 200 mg	2.04	CADTH NMA (2018)

bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drug; NMA = network meta-analysis; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

Note: The comparator csDMARD consisted of treatment with either methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine.

Source: Adapted from sponsor's pharmacoeconomic submission;[2] CADTH NMA.[4]

Summary of Key Assumptions

Table 11: Sponsor's Key Assumptions

Assumption	Comment
No treatment discontinuation was considered during the initial 3 months after treatment initiation.	Acceptable, based on clinical expert feedback.
At the end of the initial 3-month treatment response period, patients who did not respond discontinued, and a subsequent treatment was initiated.	Acceptable, based on clinical expert feedback.
No improvement or deterioration of ACR clinical response score was possible; only a discontinuation of treatment over time was considered.	Uncertain. Although the sponsor assumed that patients would not transition between ACR responses (e.g., ACR20 to ACR50) owing to a lack of data, the clinical expert consulted by CADTH stated that this was not reflective of clinical practice. The expert highlighted that patients may require an extended evaluation period (upwards of 1 year) to determine the optimal ACR response (i.e., ACR50/70) and may subsequently improve or regress during this evaluation period. Additionally, patients experiencing a lack of efficacy would likely exhibit a gradual reduction in ACR response and not immediately transition to a nonresponse as assumed by the sponsor.
Patients who responded to treatment were assumed to remain on treatment until discontinuation for any reason (e.g., loss of response or SAE) or death.	Inappropriate. The clinical expert consulted by CADTH highlighted that patients receiving injectable treatments or experiencing high pill burden may not adhere to the recommended dosing schedule. In addition, the clinical expert estimated 6% to 7% of patients may have difficulty tolerating treatment and would discontinue therapy. The clinical expert also noted that patients may receive dose reductions after maintaining a minimal ACR response over an extended duration, as treatment response was observed to be retained.

Assumption	Comment
Long-term treatment discontinuation was assumed to be equal for all treatments and only based on the level of ACR response (i.e., ACR20/50/70).	Acceptable, based on clinical expert feedback.
It was assumed patients received etanercept and infliximab approved biosimilars in Canada, as the lower costs represent a more conservative modelling approach against upadacitinib.	Acceptable.
For IV and SC injections, costs included wastage of unused medication in the vial.	Acceptable.
The worsening of HAQ scores was assumed to occur immediately after treatment withdrawal and to be reverted to the initial HAQ improvement for all treatments.	Uncertain. The clinical expert consulted by CADTH indicated that worsening HAQ scores are patient dependent and that a small proportion of patients may maintain HAQ scores until subsequent treatment; however, nonresponders would not typically experience an initial improvement in HAQ. Therefore, it was considered reasonable to apply the baseline HAQ score for nonresponders as part of CADTH's base case. This assumption was also aligned with the CADTH review of baricitinib.[5]

ACR = American College of Rheumatology; HAQ = Health Assessment Questionnaire; SAE = serious adverse event; SC = subcutaneous.

Sponsor's Results

Table 12: Results of the Sponsor's Base Case: csDMARD-IR Population

	Costs, $				QALYs			Sequential ICUR, $/QALY
	Drug	Non-drug	AE	Total	Health state	AE	Total	
Nondominated strategies								
csDMARD	75,263	2,641	865	78,769	2.31	–0.0003	2.31	-
IFX 3 mg/kg + csDMARD	83,027	2,445	754	86,225	2.41	–0.0003	2.41	74,979
ETN 50 mg + csDMARD	87,410	2,368	1,009	90,787	2.46	–0.0003	2.46	80,897
UPA 15 mg + csDMARD	91,778	2,314	1,004	95,096	2.50	–0.0003	2.50	107,659
Dominated strategies								
ETN 50 mg	88,141	2,443	972	91,556	2.41	–0.0003	2.41	Dominated
UPA 15 mg	91,476	2,349	1,020	94,844	2.47	–0.0003	2.47	Ext. dom.
BAR 2 mg + csDMARD	92,289	2,386	671	95,345	2.45	–0.0002	2.44	Dominated
TOF 5 mg + csDMARD	91,536	2,421	1,455	95,412	2.42	–0.0005	2.42	Dominated
TOF 5 mg	91,795	2,488	1,480	95,763	2.38	–0.0005	2.38	Dominated
CTZ 200 mg + csDMARD	95,659	2,377	1,039	99,074	2.45	–0.0004	2.45	Dominated
SAR 200 mg	96,450	2,471	1,440	100,361	2.39	–0.0005	2.39	Dominated
ADA 40 mg	98,311	2,577	1,014	101,902	2.33	–0.0003	2.33	Dominated
TCZ 162 mg	98,601	2,396	929	101,926	2.44	–0.0003	2.44	Dominated
GOL 50 mg + csDMARD	98,669	2,432	1,423	102,524	2.41	–0.0005	2.41	Dominated
ADA 40 mg + csDMARD	99,465	2,429	960	102,854	2.41	–0.0003	2.41	Dominated
ABT 125 mg + csDMARD	101,183	2,436	866	104,485	2.41	–0.0003	2.41	Dominated
TCZi 8 mg/kg	101,924	2,402	1,205	105,531	2.44	–0.0004	2.44	Dominated
TCZi 8 mg/kg + csDMARD	102,522	2,404	1,559	106,485	2.43	–0.0005	2.43	Dominated
ABTi 10 mg/kg + csDMARD	103,618	2,417	617	106,651	2.43	–0.0002	2.43	Dominated

	Costs, $				QALYs			Sequential ICUR, $/QALY
	Drug	Non-drug	AE	Total	Health state	AE	Total	
TOF 11 mg + csDMARD	128,319	2,377	1,439	132,135	2.46	–0.0005	2.45	Dominated
BAR 4 mg + csDMARD	130,646	2,385	448	133,480	2.45	–0.0002	2.45	Dominated

ABT = abatacept; ABTi = IV abatacept; ADA = adalimumab; AE = adverse event; BAR = baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; CTZ = certolizumab; dom. = dominated; ETN = etanercept; Ext. = extendedly; GOL = golimumab; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; SAR = sarilumab; TCZ = tocilizumab; TCZi = IV tocilizumab; TOF = tofacitinib; UPA = upadacitinib.

Note: Baricitinib 4 mg dose not currently available in Canada. "Non-drug" reflects monitoring costs. Extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Sequential ICUR = ICUR versus previous treatment listed.

Source: Adapted from sponsor's pharmacoeconomic submission.[2]

Table 13: Results of the Sponsor's Base Case: bDMARD-IR Population

	Costs, $				QALYs			Sequential ICUR, $/QALY
	Drug	Non-drug	AE	Total	Health state	AE	Total	
Nondominated strategies								
csDMARD	79,352	2,751	881	82,984	2.24	–0.0003	2.24	-
UPA 15 mg + csDMARD	93,466	2,508	1,059	97,033	2.37	–0.0004	2.37	104,193
TCZi 8 mg/kg + csDMARD	102,820	2,456	1,560	106,835	2.41	–0.0005	2.41	303,516
Dominated strategies								
TOF 5 mg + csDMARD	92,920	2,558	1,486	96,964	2.34	–0.0005	2.34	Ext. dominated
BAR 2 mg + csDMARD	94,009	2,574	723	97,306	2.33	–0.0002	2.33	Dominated
CTZ 200 mg + csDMARD	97,240	2,608	1,103	100,950	2.31	–0.0004	2.31	Dominated
SAR 200 mg + csDMARD	97,411	2,556	1,450	101,418	2.34	–0.0005	2.34	Dominated
SAR 150 mg + csDMARD	97,488	2,599	1,467	101,554	2.32	–0.0005	2.32	Dominated
GOL 50 mg + csDMARD	98,875	2,582	1,456	102,913	2.33	–0.0005	2.33	Dominated
RTX 2,000 mg + csDMARD	99,969	2,523	991	103,483	2.36	–0.0003	2.36	Dominated
ABTi 10 mg/kg + csDMARD	103,677	2,523	636	106,836	2.36	–0.0002	2.36	Dominated
TOF 11 mg + csDMARD	122,709	2,541	1,479	126,768	2.35	–0.0005	2.35	Dominated
BAR 4mg + csDMARD	126,192	2,513	478	129,183	2.36	–0.0002	2.36	Dominated

ABTi = IV abatacept; AE = adverse event; BAR = baricitinib; bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CTZ = certolizumab; Ext. = extendedly; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = IV tocilizumab; TOF = tofacitinib; UPA = upadacitinib.

Note: Baricitinib 4 mg dose not currently available in Canada. "Non-drug" reflects monitoring costs. Extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Sequential ICUR = ICUR versus previous treatment listed.

Source: Adapted from sponsor's pharmacoeconomic submission.[2]

CADTH Common Drug Review Reanalyses

Base-Case Results

Table 14: CADTH Base-Case Results: csDMARD-IR Population

Scenario	Treatment	Total costs, $	Total QALYs	Pairwise ICUR (UPA 15 mg + csDMARD vs. comparator), $/QALY	Sequential ICUR, $/QALY
CADTH base case (1+2+3+4+5+6+7)	**Nondominated strategies**				
	csDMARD	35,296	2.77	163,140	-
	ETN 50 mg + csDMARD	56,844	2.94	323,344	127,425
	UPA 15 mg + csDMARD	69,034	2.98	-	323,344
	Dominated strategies				
	IFX 3 mg/kg + csDMARD	50,896	2.89	206,186	Ext. dominated
	ETN 50 mg	54,727	2.89	158,503	Dominated by IFX 3 mg/kg + csDMARD
	ADA 40 mg	61,749	2.81	42,381	Dominated by IFX 3 mg/kg + csDMARD, ETN 50 mg, ETN 50 mg + csDMARD
	TOF 5 mg	62,011	2.86	60,015	Dominated by IFX 3 mg/kg + csDMARD, ETN 50 mg, ETN 50 mg + csDMARD
	TOF 5 mg + csDMARD	64,786	2.90	53,379	Dominated by ETN 50 mg + csDMARD
	SAR 200 mg	64,875	2.87	37,742	Dominated by IFX 3 mg/kg + csDMARD, ETN 50 mg, ETN 50 mg + csDMARD, TOF 5 mg + csDMARD
	BAR 2 mg + csDMARD	65,649	2.93	68,111	Dominated by ETN 50 mg + csDMARD
	UPA 15 mg	67,135	2.95	69,395	Ext. dominated
	TCZ 162 mg	67,443	2.92	26,284	Dominated by ETN 50 mg + csDMARD, BAR 2 mg + csDMARD, UPA 15 mg
	CTZ 200 mg + csDMARD	67,808	2.93	26,837	Dominated by ETN 50 mg + csDMARD, UPA 15 mg
	ABT 125 mg + csDMARD	68,130	2.89	10,233	Dominated by IFX 3 mg/kg + csDMARD, ETN 50 mg + csDMARD, TOF 5 mg + csDMARD, BAR 2 mg + csDMARD, UPA 15 mg, TCZ 162 mg, CTZ 200 mg + csDMARD
	ADA 40 mg + csDMARD	69,376	2.90	Dominated by UPA 15 mg + csDMARD	Dominated by ETN 50 mg + csDMARD, TOF 5 mg + csDMARD, BAR 2 mg + csDMARD, UPA 15 mg, TCZ

Scenario	Treatment	Total costs, $	Total QALYs	Pairwise ICUR (UPA 15 mg + csDMARD vs. comparator), $/QALY	Sequential ICUR, $/QALY
					162 mg, CTZ 200 mg + csDMARD, UPA 15 mg + csDMARD
	GOL 50 mg + csDMARD	70,108	2.89	Dominated by UPA 15 mg + csDMARD	Dominated by ETN 50 mg + csDMARD, TOF 5 mg + csDMARD, BAR 2 mg + csDMARD, UPA 15 mg, TCZ 162 mg, CTZ 200 mg + csDMARD, UPA 15 mg + csDMARD, ADA 40 mg + csDMARD
	TCZi 8 mg/kg	70,649	2.92	Dominated by UPA 15 mg + csDMARD	Dominated by ETN 50 mg + csDMARD, BAR 2 mg + csDMARD, UPA 15 mg, CTZ 200 mg + csDMARD, UPA 15 mg + csDMARD
	ABTi 10 mg/kg + csDMARD	70,715	2.90	Dominated by UPA 15 mg + csDMARD	Dominated by ETN 50 mg + csDMARD, BAR 2 mg + csDMARD, UPA 15 mg, TCZ 162 mg, CTZ 200 mg + csDMARD, UPA 15 mg + csDMARD, TCZi 8 mg/kg + csDMARD
	TCZi 8 mg/kg + csDMARD	71,791	2.92	Dominated by UPA 15 mg + csDMARD	Dominated by ETN 50 mg + csDMARD, BAR 2 mg + csDMARD, UPA 15 mg, TCZ 162 mg, CTZ 200 mg + csDMARD, UPA 15 mg + csDMARD
	BAR 4 mg + csDMARD	105,403	2.93	Dominated by UPA 15 mg + csDMARD	Dominated by ETN 50 mg + csDMARD, UPA 15 mg, UPA 15 mg + csDMARD
	TOF 11 mg + csDMARD	105,915	2.94	Dominated by UPA 15 mg + csDMARD	Dominated by ETN 50 mg + csDMARD, UPA 15 mg, UPA 15 mg + csDMARD

ABT = abatacept; ABTi = IV abatacept; ADA = adalimumab; BAR = baricitinib; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; CTZ = certolizumab; ETN = etanercept; Ext. = extendedly; GOL = golimumab; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; SAR = sarilumab; TCZ = tocilizumab; TCZi = IV tocilizumab; TOF = tofacitinib; UPA = upadacitinib; vs. = versus.

Note: Extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Sequential ICUR = ICUR vs. previous treatment listed.

Table 15: CADTH Base-Case Results: bDMARD-IR Population

Scenario	Treatment	Total costs, $	Total QALYs	Pairwise ICUR (UPA 15 mg + csDMARD vs. comparator), $/QALY	Sequential ICUR, $/QALY
CADTH base case (1+2+3+4+5+6+7)	**Nondominated strategies**				
	csDMARD	31,136	2.68	194,423	-
	UPA 15 mg + csDMARD	58,650	2.83	-	194,423
	TCZi 8 mg/kg + csDMARD	65,908	2.86	231,785[a]	231,785
	Dominated strategies				
	BAR 2 mg + csDMARD	54,761	2.78	85,921	Ext. dominated
	TOF 5 mg + csDMARD	55,898	2.78	64,125	Ext. dominated
	CTZ 200 mg + csDMARD	56,041	2.76	41,185	Dominated by BAR 2 mg + csDMARD, TOF 5 mg + csDMARD
	SAR 150 mg + csDMARD	56,816	2.76	29,725	Dominated by BAR 2 mg + csDMARD, TOF 5 mg + csDMARD
	SAR 200 mg + csDMARD	58,767	2.79	Dominated by UPA 15 mg + csDMARD	Dominated by UPA 15 mg + csDMARD
	GOL 50 mg + csDMARD	60,096	2.78	Dominated by UPA 15 mg + csDMARD	Dominated by BAR 2 mg + csDMARD, TOF 5 mg + csDMARD, UPA 15 mg + csDMARD, SAR 200 mg + csDMARD
	ABTi 10 mg/kg + csDMARD	63,584	2.82	Dominated by UPA 15 mg + csDMARD	Dominated by UPA 15 mg + csDMARD
	RTX 2,000 mg + csDMARD	63,701	2.81	Dominated by UPA 15 mg + csDMARD	Dominated by UPA 15 mg + csDMARD, ABTi 10 mg/kg + csDMARD
	TOF 11 mg + csDMARD	87,762	2.80	Dominated by UPA 15 mg + csDMARD	Dominated by UPA 15 mg + csDMARD, ABTi 10 mg/kg + csDMARD, RTX 2,000 mg + csDMARD, TCZi 8 mg/kg + csDMARD
	BAR 4 mg + csDMARD	89,828	2.82	Dominated by UPA 15 mg + csDMARD	Dominated by UPA 15 mg + csDMARD, ABTi 10 mg/kg + csDMARD, TCZi 8 mg/kg + csDMARD

ABTi = IV abatacept; BAR = baricitinib; bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CTZ = certolizumab; Ext. = extendedly; GOL = golimumab; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; RTX = rituximab; SAR = sarilumab; TCZi = IV tocilizumab; TOF = tofacitinib; UPA = upadacitinib; vs. = versus.

Note: Extended dominance means strategy is more costly and provides fewer QALYs than a linear combination of two other strategies. Sequential ICUR = ICUR vs. previous treatment listed.

[a] Pairwise comparison of tocilizumab 8 mg/kg + csDMARD versus upadacitinib + csDMARD.

Table 16: CADTH Base-Case Stepped Analysis

Scenario		csDMARD-IR population		bDMARD-IR population	
		Treatment	Sequential ICUR, $/QALY	Treatment	Sequential ICUR, $/QALY
	Sponsor base case	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	74,979	UPA 15 mg + csDMARD	104,193
		ETN 50 mg + csDMARD	80,897	TCZi 8 mg/kg + csDMARD	303,516
		UPA 15 mg + csDMARD	107,659		
1	Corrected sponsor base case	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	66,596	UPA 15 mg + csDMARD	106,975
		ETN 50 mg + csDMARD	99,854	TCZi 8 mg/kg + csDMARD	326,842
		UPA 15 mg + csDMARD	124,121		
2	RA patient mortality	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	68,340	UPA 15 mg + csDMARD	110,205
		ETN 50 mg + csDMARD	104,535	TCZi 8 mg/kg + csDMARD	290,326
		UPA 15 mg + csDMARD	112,258		
3	BSC costs equal to csDMARD	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	151,838	UPA 15 mg + csDMARD	197,635
		ETN 50 mg + csDMARD	163,642	TCZi 8 mg/kg + csDMARD	376,009
		UPA 15 mg + csDMARD	165,547		
4	Removal of SC and IV administration costs	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	49,108	UPA 15 mg + csDMARD	114,593
		ETN 50 mg + csDMARD	59,087	TCZi 8 mg/kg + csDMARD	153,485
		UPA 15 mg + csDMARD	236,627		
5	Equal subsequent treatment efficacy and costs	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	73,943	UPA 15 mg + csDMARD	105,691
		UPA 15 mg + csDMARD	98,376	TCZi 8 mg/kg + csDMARD	311,941
6	Baseline HAQ applied	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	65,111	UPA 15 mg + csDMARD	92,237
		ETN 50 mg + csDMARD	88,381	TCZi 8 mg/kg + csDMARD	335,278
		UPA 15 mg + csDMARD	109,529		
7	Nonlinear mapping of HAQ from Soini et al.	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	81,126	UPA 15 mg + csDMARD	115,700
		UPA 15 mg + csDMARD	117,684	TCZi 8 mg/kg + csDMARD	449,698
8	CADTH base case (1+2+3+4+5+6+7)	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	127,425	UPA 15 mg + csDMARD	194,423
		UPA 15 mg + csDMARD	323,344	TCZi 8 mg/kg + csDMARD	231,785

bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; BSC = best supportive care; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; ETN = etanercept; HAQ = Health Assessment Questionnaire; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; RA = rheumatoid arthritis; SC = subcutaneous; TCZi = IV tocilizumab; UPA = upadacitinib.

Note: Only nondominated strategies are presented. Sequential ICUR = ICUR versus previous treatment listed.

Key Scenario Results

Table 17: Results From CADTH Scenario Analyses

Scenario		csDMARD-IR population		bDMARD-IR population	
		Treatment	Sequential ICUR, $/QALY	Treatment	Sequential ICUR, $/QALY
8a	Initial HAQ score: 0.5	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	305,041	UPA 15 mg + csDMARD	434,206
		UPA 15 mg + csDMARD	778,700	TCZi 8 mg/kg + csDMARD	544,492
	Initial HAQ score: 1.0	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	184,774	UPA 15 mg + csDMARD	265,815
		ETN 50 mg + csDMARD	187,413	TCZi 8 mg/kg + csDMARD	321,302
		UPA 15 mg + csDMARD	432,987		
	Initial HAQ score: 2.0	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	102,041	UPA 15 mg + csDMARD	148,632
		UPA 15 mg + csDMARD	242,382	TCZi 8 mg/kg + csDMARD	170,503
	Initial HAQ score: 2.5	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	83,929	UPA 15 mg + csDMARD	124,244
		UPA 15 mg + csDMARD	201,692	TCZi 8 mg/kg + csDMARD	142,713
8b	HAQ score reduction: Soini et al. (2012)	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	187,889	UPA 15 mg + csDMARD	280,516
		UPA 15 mg + csDMARD	447,925	TCZi 8 mg/kg + csDMARD	323,609
	HAQ score reduction: Carlson et al. (2015)	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	161,887	UPA 15 mg + csDMARD	238,266
		UPA 15 mg + csDMARD	388,976	TCZi 8 mg/kg + csDMARD	244,237
	HAQ score reduction: Schlueter et al. (2015)	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	122,806	UPA 15 mg + csDMARD	173,105
		UPA 15 mg + csDMARD	353,634	TCZi 8 mg/kg + csDMARD	233,194
8c	Equal discontinuation rate from Carlson et al. (2015)	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	140,619	UPA 15 mg + csDMARD	206,903
		UPA 15 mg + csDMARD	356,435	TCZi 8 mg/kg + csDMARD	223,376
8d	Sponsor's costing for BSC	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	51,858	UPA 15 mg + csDMARD	116,247
		ETN 50 mg + csDMARD	59,296	TCZi 8 mg/kg + csDMARD	132,901
		UPA 15 mg + csDMARD	244,725		

Scenario		csDMARD-IR population		bDMARD-IR population	
		Treatment	Sequential ICUR, $/QALY	Treatment	Sequential ICUR, $/QALY
8e	Societal perspective	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	119,548	UPA 15 mg + csDMARD	171,169
		UPA 15 mg + csDMARD	287,839	TCZi 8 mg/kg + csDMARD	209,919
8f	No RA adjusted mortality	csDMARD	-	csDMARD	-
		ETN 50 mg + csDMARD	130,917	UPA 15 mg + csDMARD	196,495
		UPA 15 mg + csDMARD	316,268	TCZi 8 mg/kg + csDMARD	225,251
8g	20-year time horizon	csDMARD	-	csDMARD	-
		IFX 3 mg/kg + csDMARD	106,338	UPA 15 mg + csDMARD	153,700
		ETN 50 mg + csDMARD	129,296	TCZ 8 mg/kg + csDMARD	194,412
		UPA 15 mg + csDMARD	228,028		

bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; BSC = best supportive care; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; ETN = etanercept; HAQ = Health Assessment Questionnaire; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; RA = rheumatoid arthritis; TCZi = IV tocilizumab; UPA = upadacitinib.

Note: Only nondominated strategies are presented. Sequential ICUR = ICUR versus previous treatment listed.

Price Reduction Reanalyses

Table 18: CADTH Price Reduction Scenarios: csDMARD-IR Population

Scenario	Sponsor base-case ICUR, $/QALY	CADTH base-case ICUR, $/QALY
Upadacitinib submitted price	λ < 74,979: csDMARD 74,979 < λ < 80,897: IFX 3 mg/kg + csDMARD 80,897 < λ < 107,659: ETN 50 mg + csDMARD λ ≥ 107,659: UPA 15 mg + csDMARD	λ < 127,425: csDMARD 127,425 < λ < 323,425: ETN 50 mg + csDMARD λ ≥ 323,425: UPA 15 mg + csDMARD
10% reduction	λ < 62,255: csDMARD λ ≥ 62,255: UPA 15 mg + csDMARD	λ < 127,401: csDMARD 127,401 < λ < 131,664: IFX 3 mg/kg + csDMARD 131,664 < λ < 191,764: ETN 50 mg + csDMARD λ ≥ 191,764: UPA 15 mg + csDMARD
20% reduction	λ < 42,905: csDMARD **λ ≥ 42,905: UPA 15 mg + csDMARD**	λ < 121,275: csDMARD λ ≥ 121,275: UPA 15 mg + csDMARD
30% reduction	λ < 22,455: csDMARD λ ≥ 22,455: UPA 15 mg + csDMARD	λ < 102,692: csDMARD λ ≥ 102,692: UPA 15 mg + csDMARD
40% reduction	λ < 2,679: csDMARD λ ≥ 2,679: UPA 15 mg + csDMARD	λ < 79,346: csDMARD λ ≥ 79,346: UPA 15 mg + csDMARD
50% reduction	All comparators and UPA monotherapy dominated by UPA 15 mg + csDMARD	λ < 59,365: csDMARD λ ≥ 59,365: UPA 15 mg + csDMARD
60% reduction	All comparators and UPA monotherapy dominated by UPA 15 mg + csDMARD	λ < 39,102: csDMARD **λ ≥ 39,102: UPA 15 mg + csDMARD**

λ = willingness-to-pay threshold; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; ETN = etanercept; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; UPA = upadacitinib.

Note: Only nondominated strategies are presented.

Table 19: CADTH Price Reduction Scenarios: bDMARD-IR Population

Scenario	Sponsor base-case ICUR, $/QALY	CADTH base-case ICUR, $/QALY
Upadacitinib submitted price	λ < 104,193: csDMARD 104,193 < λ < 303,516: UPA 15 mg + csDMARD λ ≥ 303,516: TCZi 8 mg/kg + csDMARD	λ < 194,425: csDMARD 194,425 < λ < 231,785: UPA 15 mg + csDMARD λ ≥ 231,785: TCZi 8 mg/kg + csDMARD
10% reduction	λ < 85,598: csDMARD 85,598 < λ < 375,269: UPA 15 mg + csDMARD λ ≥ 375,269: TCZi 8 mg/kg + csDMARD	λ < 169,909: csDMARD 169,909 < λ < 298,693: UPA 15 mg + csDMARD λ ≥ 298,693: TCZi 8 mg/kg + csDMARD
20% reduction	λ < 56,350: csDMARD 56,350 < λ < 562,990: UPA 15 mg + csDMARD λ ≥ 562,990: TCZi 8 mg/kg + csDMARD	λ < 141,702: csDMARD 141,702 < λ < 475,993: UPA 15 mg + csDMARD λ ≥ 475,993: TCZi 8 mg/kg + csDMARD
30% reduction	λ < 36,926: csDMARD **36,926 < λ < 578,049: UPA 15 mg + csDMARD** λ ≥ 578,049: TCZi 8 mg/kg + csDMARD	λ < 121,689: csDMARD 121,689 < λ < 597,853: UPA 15 mg + csDMARD λ ≥ 597,853: TCZi 8 mg/kg + csDMARD
40% reduction	λ < 17,581: csDMARD 17,581 < λ < 752,160: UPA 15 mg + csDMARD λ ≥ 752,160: TCZi 8 mg/kg + csDMARD	λ < 100,009: csDMARD 100,009 < λ < 578,303: UPA 15 mg + csDMARD λ ≥ 578,303: TCZi 8 mg/kg + csDMARD
50% reduction	λ < 813,707: UPA 15 mg + csDMARD λ ≥ 813,707: TCZi 8 mg/kg + csDMARD	λ < 79,967: csDMARD 79,967 < λ < 724,222: UPA 15 mg + csDMARD λ ≥ 724,222: TCZi 8 mg/kg + csDMARD
60% reduction	λ < 1,192,644: UPA 15 mg + csDMARD λ ≥ 1,192,644: TCZi 8 mg/kg + csDMARD	λ < 53,714: csDMARD 53,714 < λ < 924,946: UPA 15 mg + csDMARD λ ≥ 924,946: TCZi 8 mg/kg + csDMARD
70% reduction	λ < 1,085,156: UPA 15 mg + csDMARD λ ≥ 1,085,156: TCZi 8 mg/kg + csDMARD	λ < 31,529: csDMARD **31,529 < λ < 825,714: UPA 15 mg + csDMARD** λ ≥ 825,714: TCZi 8 mg/kg + csDMARD

λ = willingness-to-pay threshold; bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZi = IV tocilizumab; UPA = upadacitinib.

Note: Only nondominated strategies are presented.

Price Reduction Scenarios

Table 20: CADTH Base-Case Results (No csDMARD)

Scenario	Treatment	Total costs, $	Total QALYs	Sequential ICUR, $/QALY
CADTH base case (1+2+3+4+5+6+7)	**csDMARD-IR**			
	IFX 3 mg/kg + csDMARD	50,840	2.89	-
	ETN 50 mg + csDMARD	56,738	2.93	125,267
	UPA 15 mg + csDMARD	68,939	2.97	325,231
	bDMARD-IR			
	BAR 2 mg + csDMARD	55,029	2.78	-

Scenario	Treatment	Total costs, $	Total QALYs	Sequential ICUR, $/QALY
	UPA 15 mg + csDMARD	58,988	2.84	78,225
	TCZi 8 mg/kg + csDMARD	66,598	2.87	228,154

BAR = baricitinib; bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; ETN = etanercept; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; TCZi = intravenous tocilizumab; UPA = upadacitinib.

Note: Only nondominated strategies are presented. Sequential ICUR = ICUR versus previous treatment listed.

Table 21: CADTH Price Reduction Scenarios: csDMARD-IR Population (No csDMARD)

Scenario	Sponsor base-case ICUR, $/QALY	CADTH base-case ICUR, $/QALY
Upadacitinib submitted price	λ < 106,033: IFX 3 mg/kg + csDMARD λ ≥ 106,033: UPA 15 mg + csDMARD	λ < 125,266: IFX 3 mg/kg + csDMARD 125,266 < λ < 325,231: ETN 50 mg + csDMARD λ ≥ 325,231: UPA 15 mg + csDMARD
10% reduction	λ < 54,586: IFX 3 mg/kg + csDMARD λ ≥ 54,586: UPA 15 mg + csDMARD	λ < 118,661: IFX 3 mg/kg + csDMARD 118,661 < λ < 202,382: ETN 50 mg + csDMARD λ ≥ 202,382 UPA 15 mg + csDMARD
20% reduction	λ < 7,991: IFX 3 mg/kg + csDMARD **λ ≥ 7,991: UPA 15 mg + csDMARD**	λ < 110,351: IFX 3 mg/kg + csDMARD λ ≥ 110,351: UPA 15 mg + csDMARD
30% reduction	All comparators and UPA monotherapy dominated by UPA 15 mg + csDMARD	λ < 54,380: IFX 3 mg/kg + csDMARD λ ≥ 54,380: UPA 15 mg + csDMARD
35% reduction	All comparators and UPA monotherapy dominated by UPA 15 mg + csDMARD	λ < 28,350: IFX 3 mg/kg + csDMARD **28,350 < λ < 44,015: UPA 15 mg** **λ ≥ 44,015: UPA 15 mg + csDMARD**

λ = willingness-to-pay threshold; csDMARD = conventional synthetic disease-modifying antirheumatic drug; csDMARD-IR = responded inadequately or are intolerant to one or more csDMARDs; ETN = etanercept; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; UPA = upadacitinib.

Note: Only nondominated strategies are presented.

Table 22: CADTH Price Reduction Scenarios: bDMARD-IR Population (No csDMARD)

Scenario	Sponsor base-case ICUR, $/QALY	CADTH base-case ICUR, $/QALY
Upadacitinib submitted price	λ < 2,949: TOF 5 mg + csDMARD **2,949 < λ < 279,110: UPA 15 mg + csDMARD** λ ≥ 279,110: TCZi 8 mg/kg + csDMARD	λ < 78,225: BAR 2 mg + csDMARD 78,225 < λ < 228,154: UPA 15 mg + csDMARD λ ≥ 228,154: TCZi 8 mg/kg + csDMARD
5% reduction	λ < 369,270: UPA 15 mg + csDMARD λ ≥ 369,270: TCZi 8 mg/kg + csDMARD	λ < 43,932: BAR 2 mg + csDMARD **43,932 < λ < 280,069: UPA 15 mg + csDMARD** λ ≥ 280,069: TCZi 8 mg/kg + csDMARD

λ = willingness-to-pay threshold; BAR = baricitinib; bDMARD-IR = responded inadequately or are intolerant to one or more biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TCZi = intravenous tocilizumab; TOF = tofacitinib; UPA = upadacitinib.

Note: Only nondominated strategies are presented.

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