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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

TOFACITINIB (XELJANZ)

(Pfizer Canada Inc.)

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response, or intolerance to either conventional UC therapy or a tumour necrosis factor alpha inhibitor.

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	March 2019
Report Length:	41 Pages

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

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

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Table of Contents

Tables

Figure

CADTH

Abbreviations

AE	adverse event
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
QALY	quality-adjusted life-year
UC	ulcerative colitis
URTI	upper respiratory tract infection

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Tofacitinib (Xeljanz)
Study Question	What is the cost-effectiveness of tofacitinib versus biological agents or conventional therapy for patients with moderately to severely active ulcerative colitis following an inadequate response, loss of response, or intolerance to either conventional therapy or a biological agent?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients (≥ 18 years of age) with moderately to severely active ulcerative colitis with an inadequate response to conventional therapy or biological agent (i.e., biologic-naive or biologic-exposed)
Treatment	Tofacitinib 10 mg twice daily for induction (8 weeks), followed by 5 mg twice daily for maintenance, added to conventional therapy (i.e., aminosalicylates and/or corticosteroids)
Outcome	Quality-adjusted life-years (QALYs)
Comparators	• Vedolizumab (Entyvio) • Infliximab (Remicade, biosimilar) • Adalimumab (Humira) • Golimumab (Simponi) • Continuing conventional therapy (combination of aminosalicylates, corticosteroids, and immunomodulators)
Perspective	Canadian public health care payer
Time Horizon	Lifetime (60 years for a 41-year-old individual)
Results for Base Case	ICURs were presented as pairwise comparisons of tofacitinib vs. each comparator: • Tofacitinib vs. vedolizumab, infliximab, or golimumab: dominant (lower costs, higher QALYs) • Tofacitinib vs. adalimumab: $8,897 per QALY gained • Tofacitinib vs. infliximab biosimilar: $145,184 per QALY gained • Tofacitinib vs. conventional therapy: $118,387 per QALY gained
Key Limitations	• The comparative treatment effects of tofacitinib with relevant comparators, particularly in the maintenance phase, are uncertain given the limitations of the tofacitinib studies and the manufacturer-submitted ITC identified by CADTH clinical reviewers • Modelling of treatment sequences in biologic-naive patients was biased against comparator treatments due to inclusion of a different second-line of treatment for tofacitinib vs. certain comparator treatments • The post-colectomy health state utility value was lower than the utility value for patients with active ulcerative colitis, which does not appear to be appropriate (does not meet face validity) • Adverse event risks were applied only in the 8-week induction phase despite evidence of adverse events occurring in the maintenance studies
CDR Estimates	CADTH reanalyses were conducted separately for biologic-naive and -exposed patients: • For biologic-naive patients, tofacitinib was dominated by infliximab biosimilar, which is less costly and associated with more QALYs than tofacitinib • For biologic-exposed patients conventional therapy is the optimal therapy at a willingness-to-pay of less than $143,710 and tofacitinib is the optimal therapy at a willingness-to-pay greater than $143,710 • Price reductions of 44% and 74% would be required for tofacitinib to be a cost-effective treatment at a willingness-to-pay of $50,000 per QALY in the biologic-exposed and biologic-naive populations, respectively, in comparison with conventional UC therapy

CDR = CADTH Common Drug Review; ICUR = Incremental cost-utility ratio; ITC = indirect treatment comparison; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Drug	Tofacitinib (Xeljanz)
Indication	For the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a tumour necrosis factor alpha inhibitor
Reimbursement Request	As per indication
Dosage Form	Tofacitinib tablets 5 mg and 10 mg (as tofacitinib citrate)
NOC Date	September 11, 2018
Manufacturer	Pfizer Canada Inc.

Executive Summary

Background

Tofacitinib (Xeljanz) is an orally administered Janus kinase inhibitor indicated for the treatment of patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response, or intolerance to either conventional UC therapy or a biologic agent.[1] The recommended dosage for tofacitinib is one 10 mg tablet administered twice daily during an induction period lasting at least eight weeks, followed by one 5 mg tablet administered twice daily thereafter during the maintenance phase of treatment once response to treatment has been achieved. Tofacitinib 10 mg twice daily in the maintenance phase may be prescribed to some patients.[2] The product monograph states that tofacitinib should be discontinued if no evidence of benefit is achieved by week 16. At the manufacturer-submitted price of $23.96 per 5 mg tablet and $42.34 per 10 mg tablet,[1] the annual cost of tofacitinib is $19,501 in the first year and $17,442 every year thereafter, based on the recommended dosage for induction and 5 mg twice daily in the maintenance phase. This cost could increase significantly, up to $30,181 per year, in certain populations requiring tofacitinib 10 mg twice daily in the maintenance phase.

Tofacitinib 5 mg was previously considered by CADTH Canadian Drug Expert Committee for the treatment of rheumatoid arthritis in 2015 and was recommended to be listed with clinical criteria, with the condition that the drug plan cost for tofacitinib not exceed the drug plan costs for the biologic disease-modifying antirheumatic drugs.[3]

The manufacturer submitted a cost-utility analysis comparing tofacitinib plus conventional therapy (a mix of 5-aminosalicylates, corticosteroids, and immunomodulators) with biologic treatments (vedolizumab, infliximab, infliximab biosimilar, adalimumab, and golimumab) plus conventional therapy (same as tofacitinib), as well as continuing conventional therapy (the same mix of 5-aminosalicylates, steroids, and immunomodulators) in patients (≥ 18 years of age) with moderately to severely active UC and an inadequate response to conventional therapy or biological agents. The analysis was conducted over a lifetime time horizon from a Canadian public health care payer perspective. The manufacturer submitted a cohort-level state-transition (Markov) model, in which patients entered the model in an active UC state and started an eight-week induction period with tofacitinib or a biologic comparator plus conventional therapy or continued on conventional therapy alone. At any time in the model,

patients could experience a response or clinical remission, or remain in an active UC state (nonresponders), and patients in a clinical remission or response state could lose their response and regress to active UC. Patients in the active UC state could undergo a colectomy at any point; the risk of colectomy differed based on time since UC diagnosis.[1] Two populations were modelled separately: patients who had previously received biologic treatment (biologic-exposed) or patients who had not previously received biologic treatment (biologic-naive). The two groups were combined into a weighted mixed population analysis (53.9% biologic-exposed and 46.1% biologic-naive patients as observed in the manufacturer's induction trials). Biologic-naive patients who did not respond to tofacitinib or biologic treatment were switched to a different biologic agent (vedolizumab in all cases, with the exception of infliximab for patients starting on vedolizumab) prior to conventional therapy if they did not respond to the second biologic agent. Biologic-exposed patients who did not respond to tofacitinib or biologic treatment received conventional therapy. An indirect treatment comparison submitted by the manufacturer was used to inform the treatment efficacy of tofacitinib and all included comparators.[4] The health state utilities for response, clinical remission and active UC were derived from the manufacturer's OCTAVE trials, while disutilities for adverse events (AEs) and utility values for the post-colectomy health state were identified from the literature. All analyses were conducted pairwise between tofacitinib and each comparator.

When compared with adalimumab, infliximab biosimilar, and continuing conventional UC therapy for a mixed population of biologic-exposed and -naive patients, tofacitinib had higher costs and quality-adjusted life-years (QALYs), resulting in incremental cost-utility ratios (ICURs) of $8,897, $145,184, and $118,387 per QALY gained, respectively. The manufacturer reported tofacitinib was dominant (fewer costs, increased QALYs) when compared with vedolizumab, infliximab, and golimumab. When reporting results by previous exposure to biologics, results for biologic-naive patients were similar to the mixed population, although the ICUR for tofacitinib in comparison with infliximab biosimilar increased substantially ($1,101,156 per QALY). In biologic-exposed patients, tofacitinib was no longer dominant compared with golimumab (ICUR: $1,388 per QALY). In other results the treatment-exposed population was similar to the mixed population. CADTH reanalyzed the manufacturer's results as sequential analyses, which found that for the manufacturer's base case, tofacitinib was not a cost-effective option at a willingness-to-pay of $100,000 per QALY.

Summary of Identified Limitations and Key Results

CADTH identified several key limitations with the manufacturer's economic evaluation.

There is considerable uncertainty regarding the comparative treatment effect for tofacitinib. CADTH clinical reviewers critically appraised the manufacturer's indirect treatment comparison and noted several limitations, in particular the methods related to the treat-through analysis of maintenance-phase trials that were used to inform the economic model. Furthermore, the efficacy observed at 52 weeks in the maintenance phase was assumed to persist for the rest of the time horizon. This is unlikely to be the case according to the clinical experts consulted by CADTH and potentially favoured the treatments with greater treatment efficacy, including tofacitinib. No changes could be made to the manufacturer's model to address issues of clinical uncertainty.

The manufacturer's base case included a second-line treatment option for patients who were biologic-naive. The inclusion of a second-line of treatment for biologic-naive patients

complicates the interpretation of the results in terms of the benefits attributed to which treatment. A potential for bias against some comparators exists, given the choice of subsequent therapy, both in terms of costs and treatment efficacy.

The manufacturer used a utility value for post-colectomy remission that was lower than the utility value for patients with active UC. This was deemed to lack face validity as it is unlikely that colectomy would be performed if it leads to worse outcomes (e.g. reduced quality of life) for patients.

AE risks in the manufacturer's model were only applied in the induction phase. This was identified to be unlikely in clinical practice as indicated by the AEs reported in the maintenance studies of each comparator. In addition, the risks considered for upper respiratory tract infections, serious infections, and malignancies varied notably depending on treatment. However, data for AEs were derived from efficacy trials for each comparator not powered for safety with heterogeneous populations, none of the rates obtained were adjusted for baseline risks in the control groups, and no observational data were considered. Additionally, feedback from the clinical experts consulted by CADTH suggested significant differences in these events are not observed in clinical practice. The same clinical experts also noted concern regarding the increased risk of *Herpes zoster* in patients receiving tofacitinib 10 mg twice daily in the maintenance phase.

The product monograph indicates tofacitinib should be discontinued in patients who show no evidence of adequate therapeutic benefit by week 16, while the manufacturer's base case assumes an induction period of eight weeks. A shorter induction period may underestimate the drug costs associated with tofacitinib, improving its cost-effectiveness relative to other comparators. CADTH conducted a scenario analysis in which the induction period was extended to 16 weeks per information in the product monograph.[2] The clinical expert consulted by CADTH indicated that eight weeks should be sufficient to determine treatment response with tofacitinib, so this was left in as the induction period in the CADTH base case.

CADTH undertook reanalyses of the manufacturer's model to address some of the identified limitations. To better represent the nuances with how tofacitinib is likely to be used in Canadian clinical practice, CADTH undertook two base-case analyses, one for biologic-naive patients and another for biologic-exposed patients. The revised base cases incorporated a more appropriate utility value for post-colectomy. They also applied the same AE risk for upper respiratory tract infections, serious infections, and malignancies, and applied AE risks in all model cycles. Additional scenario analyses that tested removal of the second-line of biologic treatment, the impact of dosing, increased risk of *H. zoste*r, alternative conventional therapy distribution, and extending the induction period to 16 weeks were undertaken on the individual populations; exploratory analyses were conducted on the mixed population.

The CADTH base case for biologic-naive patients determined continuing conventional UC therapy to be the least costly and least effective of the comparators. Infliximab biosimilar had an ICUR versus conventional UC therapy of $166,608 per QALY gained, and all other medications, including tofacitinib, were dominated by (i.e., less effective and more costly than) infliximab biosimilar.

The CADTH base case for biologic-exposed patients found continuing conventional UC therapy to be the least costly and least effective of the comparators; tofacitinib was the only non-dominated therapy. If a decision maker's willingness-to-pay is no more than $143,710

per QALY, conventional UC therapy would be the optimal therapy; at a willingness-to-pay greater than $143,710 per QALY tofacitinib would be the optimal therapy.

If the efficacy and safety of tofacitinib is assumed to be equivalent to the biologic comparators and used according to the product monograph dosing recommendations, the annual cost of tofacitinib is greater than the annual cost of at least one of the direct comparators based on publicly available prices (Table 10).

Conclusions

CADTH conducted reanalyses in the biologic-exposed and biologic-naive populations separately to address some of the key limitations. In the biologic-naive population, CADTH found that tofacitinib was more costly and less effective than infliximab biosimilar. Infliximab biosimilar remains more effective than tofacitinib in all price-reduction scenarios, but a price reduction of 74% for tofacitinib would make tofacitinib less costly, and the ICUR for infliximab biosimilar compared with tofacitinib would increase to more than $50,000 per QALY.

In the biologic-exposed population, tofacitinib was found to be the optimal therapy at a willingness-to-pay above $143,710. When compared with conventional UC therapy, a price reduction of 44% would be required for tofacitinib to be cost-effective at a willingness-to-pay of $50,000 per QALY in the biologic-exposed population.

CADTH reanalyses could not address several important limitations, including those related to treatment efficacy and duration of treatment effect, and as such, the results of this economic evaluation should be viewed with caution.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis of tofacitinib added to conventional therapy (mix of 5-aminosalicylates, corticosteroids, and immunomodulators) versus biologics (vedolizumab, infliximab, infliximab biosimilar, adalimumab, and golimumab) added to conventional therapy and continuing conventional therapy alone (same mix of 5-aminosalicylates, corticosteroids, and immunomodulators) in Canadian adults (≥ 18 years of age) with moderately to severely active ulcerative colitis (UC) following an inadequate response to conventional therapy or a biologic. The analysis was conducted over a lifetime time horizon (approximately 60 years for a 41-year-old adult), conducted from a Canadian public health care payer perspective using a cohort-level state-transition model programmed in Microsoft Excel. The model was designed to reflect the clinical practice and disease progression of UC according to the manufacturer.[1] At baseline, the patient cohort was made up of both biologic-naive (46.1%) and biologic-exposed (53.9%) patients who were predominantly male (59.2%), and had the disease for three years on average. Patients entered the model with active UC and underwent an eight-week treatment induction phase with either tofacitinib or a biologic, or continued conventional therapy. Following this eight-week induction phase, patients responding to treatment could move into one of two maintenance-phase health states (response or clinical remission), or they could die or have a colectomy.[1] Response was defined as a decrease from baseline Mayo score of at least three points and at least 30%, with a decrease in rectal bleeding subscore of at least one point or absolute rectal bleeding subscore of 0 or 1. Clinical remission was defined as a total Mayo score of ≤ 2, with no individual subscore exceeding 1. Patients who did not achieve response or clinical remission at the end of the eight-week induction period, but remained alive and colectomy-free, switched treatments and followed a similar sequence of treatment induction and potential response (Figure 1).

Patients who achieved a response remained in the maintenance phase and could transition between response and clinical remission until loss of response, at which point they could switch to another biologic as long as they were biologic treatment-naive. Patients who did not respond to their initial treatment and were biologic-exposed or biologic-naive patients not responding to their second modelled treatment then switched to conventional therapy alone, with the possibility of responding to treatment in a maintenance health state or remaining in an active UC state until their death or until they had a colectomy.[1] Patients starting on conventional therapy did not transition to another medication over the duration of the model, but they could transition to receiving a colectomy. Additionally, patients could die at any point, but only patients in an active UC state could experience a colectomy and move to a post-surgery health sate. Following one of two potential surgery types (total colectomy with end ileostomy or restorative colectomy), patients could be in one of two post-surgery states specific to the surgery type (i.e., complications or no complications), where they either remained or transitioned between until their death.[1]

In the model, treatment efficacy was applied through transition probabilities between health states. Data from a manufacturer-funded indirect treatment comparison (ITC), specifically, the difference in probits between conventional therapy and comparator treatments, were used to inform the transition probabilities.[4] Different sets of values were generated for the

biologic-naive and -exposed populations, with the model stratifying the analysis by population and results aggregated using a weighted average based on the proportion of patients in each population. Additionally, separate transition probabilities were derived for induction and maintenance phases and by time point in the maintenance phase (i.e., baseline, 24 weeks and 52 weeks). The risk inputs for each potential adverse event (AE) were not obtained from the ITC and were instead obtained from the intention-to-treat populations from each of the induction and maintenance phases of efficacy trials for each comparator. Risk of colectomy was obtained from a Canadian registry study[5] and mortality risk was obtained from World Health Organization life tables for Canada.[6]

Utility weights for the modelled health states were obtained from several different sources. Utility weights for the clinical remission, response without remission, and no-response health states were derived from the OCTAVE 1 and 2 trials for the induction phase, and from the OCTAVE Sustain trial in the maintenance phase.[1] Utility weights for the post-colectomy state and disutilities due to AEs were sourced from previous health technology assessment reports[3] and published literature.[7]

Resource use by health state was informed by a study from Tsai et al.,[8] while the costs for such resource use were obtained from Canadian sources.[9,10] Information on dosing regimens for each comparator were obtained from their respective product monographs, while the drug and administration costs, and costs related to AEs from medications, were obtained from Canadian sources.[11,10]

Manufacturer's Base Case

The manufacturer reported its results only as pairwise comparisons and not sequentially. In the manufacturer's base case (for a mixed population of biologic-naive and biologic-exposed patients), tofacitinib was dominant (fewer costs, more quality-adjusted life-years [QALYs]) when compared with vedolizumab, infliximab, or golimumab. When compared with adalimumab, infliximab biosimilar, and conventional UC therapy, tofacitinib had higher costs and higher QALYs, resulting in incremental cost-utility ratios (ICURs) of $8,897, $145,184, and $118,387 per QALY gained, respectively (Table 2).

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

	Total Costs	Incremental Cost (Tofacitinib vs. Comparator)	Total QALYs	Incremental QALYs (Tofacitinib vs. Comparator)	Incremental Cost per QALY (Tofacitinib vs. Comparator)
Tofacitinib	$603,226	ref	23.787	ref	ref
Adalimumab	$602,527	$699	23.708	0.079	$8,897
Conventional UC therapy	$583,942	$19,285	23.624	0.163	$118,387
Golimumab	$604,495	−$1,269	23.743	0.044	Dominant
Infliximab biosimilar	$601,283	$1,944	23.774	0.013	$145,184
Infliximab	$616,571	−$13,344	23.773	0.014	Dominant
Vedolizumab	$612,779	−$9,552	23.765	0.022	Dominant

QALY = quality-adjusted life-year; UC = ulcerative colitis.

Source: Manufacturer's pharmacoeconomic submission.[1]

CADTH has presented the results in the form of a sequential analysis based on the recommendations in the most recent guidelines for the economic evaluation of health technologies in Canada.[12] The sequential analysis based on the manufacturer's base-case results indicate that continuing conventional therapy alone would be cost-effective up to a willingness-to-pay of $115,606 per QALY; infliximab biosimilar would be cost-effective if a decision-maker was willing to pay between $115,606 to $149,461 per QALY; and tofacitinib would be cost-effective at a willingness-to-pay of $149,461 per QALY or above (Table 3).

Table 3: Summary of Results of the Manufacturer's Base Case — Sequential Analysis

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$583,942	23.624		
Infliximab biosimilar	$601,283	23.774	$115,606	$115,606
Tofacitinib	$603,226	23.787	$118,306	$149,461
Adalimumab	$602,527	23.708	$221,250	Dominated by infliximab biosimilar
Golimumab	$604,495	23.743	$172,714	Dominated by tofacitinib and infliximab biosimilar
Vedolizumab	$612,779	23.765	$204,518	Dominated by tofacitinib and infliximab biosimilar
Infliximab	$616,571	23.773	$218,986	Dominated by tofacitinib and infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Note: Total costs and QALYs are as reported in Table 2, based on 1,000 simulations.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[1]

The manufacturer's base-case results were undertaken using 1,000 simulations and the results were not stable. CADTH therefore conducted an analysis using the manufacturer's base case with 5,000 simulations. Several runs using 5,000 simulations were conducted to ensure results were robust and consistently similar at this number of iterations. Within this analysis using the manufacturer's base case at 5,000 simulations, conventional therapy alone was found to be cost-effective up to a willingness-to-pay of $117,142 per QALY, infliximab biosimilar would be the optimal therapy should a decision-maker be willing to pay between $117,142 and $148,615 per QALY, and tofacitinib would be the optimal therapy at a willingness-to-pay above $148,615. All other comparators were dominated by infliximab biosimilar (Table 4) based on the manufacturer's base case, analyzed sequentially over 5,000 simulations.

Table 4: Summary of Results of the Manufacturer's Base Case with 5,000 Simulations — Sequential Analysis

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$583,923	23.635		
Infliximab biosimilar	$601,260	23.783	$117,142	$117,142
Tofacitinib	$603,192	23.796	$119,683	$148,615
Adalimumab	$602,491	23.719	$221,048	Dominated by infliximab biosimilar
Golimumab	$604,440	23.753	$173,873	Dominated by tofacitinib and infliximab biosimilar
Vedolizumab	$612,749	23.776	$204,440	Dominated by tofacitinib and infliximab biosimilar
Infliximab	$616,516	23.782	$221,721	Dominated by tofacitinib and infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[1]

Summary of Manufacturer's Scenario Analyses

When reporting results by previous exposure to biologics, results were similar for biologic-naive patients except for the ICUR in comparison with infliximab biosimilar ($1,101,156 per QALY; Table 15). For biologic-exposed patients, tofacitinib continued to dominate vedolizumab and infliximab, but it was no longer dominant compared with golimumab (ICUR: $1,388 per QALY). The ICUR for tofacitinib compared with adalimumab rose to $24,843 per QALY, while the ICURs compared with infliximab biosimilar and continuing conventional therapy decreased to $14,622 and $98,625 per QALY, respectively (Table 16).

CADTH also analyzed these subgroup analyses sequentially. A summary of results for biologic-naive patients is available in Table 5, while a summary of results for biologic-exposed patients is available in Table 6. These results are based on the manufacturer-provided analyses, and were not run at 5,000 simulations.

Table 5: Summary of Results of the Manufacturer's Subgroup Analyses — Biologic-Naive (Sequential Analysis)

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$582,289	23.658		
Infliximab biosimilar	$609,325	23.895	$114,076	$114,076
Adalimumab	$612,912	23.784	$243,040	Dominated by infliximab biosimilar
Tofacitinib	$613,063	23.898	$128,225	Dominated by infliximab biosimilar
Golimumab	$615,765	23.784	$265,683	Dominated by tofacitinib and infliximab biosimilar

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Vedolizumab	$626,134	23.882	$195,737	Dominated by tofacitinib and infliximab biosimilar
Infliximab	$630,844	23.896	$204,013	Dominated by tofacitinib and infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Note: Total costs and QALYs are as reported in Table 15, based on 1,000 simulations.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[1]

Table 6: Summary of Results of the Manufacturer's Subgroup Analyses — Biologic-Exposed (Sequential Analysis)

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$584,333	23.618		
Tofacitinib	$593,813	23.714	$98,750	$98,750
Adalimumab	$592,579	23.664	$179,261	Subject to extended dominance through conventional UC therapy and tofacitinib
Infliximab biosimilar	$593,400	23.686	$133,338	Subject to extended dominance through conventional UC therapy and tofacitinib
Golimumab	$593,762	23.677	$159,814	Dominated by tofacitinib and infliximab biosimilar
Vedolizumab	$600,470	23.689	$227,282	Dominated by tofacitinib
Infliximab	$603,318	23.676	$327,328	Dominated by tofacitinib, infliximab biosimilar, and vedolizumab

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Note: Total costs and QALYs are as reported in Table 16, based on 1,000 simulations.

Source: Adapted from the manufacturer's pharmacoeconomic submission.[1]

Summary of Manufacturer's Sensitivity Analyses

In the manufacturer's deterministic sensitivity analyses, treatment efficacy and the utility of post-colectomy were identified as key drivers in the model. When the treatment efficacy for the biologic and conventional UC therapies was increased and decreased using the upper- and lower-bound values of the 95% credible intervals, tofacitinib was dominated by infliximab biosimilar in the upper-bound case while dominating adalimumab in the lower-bound case. The ICUR for tofacitinib when compared with conventional UC therapy increased ($226,303 per QALY) and decreased ($111,105 per QALY) relative to the reference case ICUR ($119,435) in the upper and lower cases, respectively, while tofacitinib was less costly and less effective than the rest of the comparators in all other cases.

When the upper and lower ranges in the utility following colectomy were tested, ICURs for the non-dominated comparators (adalimumab, infliximab biosimilar, and conventional UC therapy) increased and decreased when the upper- and lower-bound utility value were used, respectively (see Appendix 3, Table 17). All other alternative biologics remained dominated.

Limitations of Manufacturer's Submission

- **Incorporation of subsequent treatments for biologic-naive may bias against comparator treatments:** The manufacturer modelled two lines of biologic treatment for patients who were biologic-naive upon entering the model. While multiple biologics are used following treatment failure and the inclusion of a second-line of treatment would be reflective of current practice, the inclusion of subsequent treatments introduces additional uncertainty into the model. Inclusion of a second-line treatment for biologic-naive patients convolutes the benefit achieved by the sequential treatments as the benefits and costs are attributed in part to the second biologic, and as such choice of the second biologic could significantly influence the results. For example, patients initially receiving vedolizumab received infliximab as a second-line treatment, while all other comparators received vedolizumab as the second-line treatment. Based on the manufacturer's inputs, infliximab has a lower efficacy than vedolizumab in the maintenance phase, and the treatment strategy starting with vedolizumab is therefore more likely to lead to lower QALYs given the choice of a second biologic. To address this, CADTH considered removing a biologic or tofacitinib as a second-line treatment for biologic-naive patients. However, additional uncertainty was identified in the model when removing second-line biologic therapy in biologic-naive patients, as this increased the total QALYs for these patients while increasing total costs. As such, conventional therapy became less attractive with this consideration. CADTH could not reliably test the impact of removing this parameter.
- **Comparative treatment efficacy is uncertain:** The manufacturer incorporated results from the treat-through analysis of its ITC to inform transition probabilities and treatment efficacy within the economic model for the maintenance phase. Based on the appraisal of the ITC by CADTH clinical reviewers, there are concerns with the methods used in the treat-through analysis, as the ITC authors relied on imputed data for tofacitinib and golimumab. The imputation method required separating patients into subgroups based on their response after treatment induction and thus randomization was not maintained. Additionally, while some of the imputation methods used had been published, the CADTH appraisal of the ITC noted that other imputation methods developed by the ITC authors incorporated arbitrary assumptions, and that none of the imputation methods had been validated. Overall, CADTH clinical reviewers concluded there were no statistically significant differences between tofacitinib and infliximab, adalimumab, golimumab, or

vedolizumab for the induction phase in patients with no prior anti–tumour necrosis factor treatment experience. However, no conclusions could be drawn with regard to the efficacy of tofacitinib for induction therapy in patients who were anti–tumour necrosis factor treatment–experienced, or in either population for the maintenance population, due to sparse data or differences in study design and populations enrolled.

- Also of note with the treatment efficacy is the assumption that treatment response remained constant indefinitely beyond 52 weeks in the maintenance phase. The clinical experts consulted by CADTH for this review noted that this is unlikely and that treatment waning is expected over time, particularly in patients in only partial remission.
- CADTH was unable to address either of these issues with treatment efficacy in the CADTH reanalyses but notes that there is considerable uncertainty with treatment efficacy and that the model currently favours tofacitinib due to improved treatment outcomes from higher treatment efficacy relative to other comparators, based on the results of the treat-through population from the ITC.
- **Utility value for remission post-surgery lacks face validity:** The utility value for remission post-colectomy in the manufacturer's base case is 0.67, which is lower than the value for active UC (0.687 in induction, 0.783 in maintenance). This lacks face validity, as on average patients post-colectomy would expect to have a utility value that is higher than active UC without response or remission in the maintenance phase. Given the manufacturer health states and corresponding utilities, CADTH considered an alternate post-colectomy value of 0.79, which was identified in the literature from a study of patients who received a colectomy in Canada, the UK, or Australia.[13] This value was elicited using the EuroQol 5-Dimensions questionnaire index, which is the same scale used for the health state utilities in the manufacturer-submitted model. This value was applied in the CADTH base cases.
- **Identification of adverse event risks:** The manufacturer obtained risk inputs for AEs from the number of patients with each event among the intention-to-treat population of the induction and maintenance efficacy trials for each included treatment comparator, as the ITC did not have enough data to assess relative treatment safety between comparators. The trials used to inform the AE risks were efficacy studies and likely not powered to identify AEs. Additionally, these risks were not adjusted for the event rates in the placebo groups in their respective trials. Serious infections, upper respiratory tract infections (URTIs), and malignancies were assumed to occur at lower rates for tofacitinib relative to some of its comparators, and as such likely biased costs and QALYs in favour of tofacitinib. The clinical experts consulted by CADTH noted that the AE risks for URTIs, malignancies, and serious infections were unlikely to be different between comparators. Additionally, there was some concern noted by the clinical expert consulted by CADTH with the higher *Herpes zoster* risk in the 10 mg arm of the OCTAVE Sustain maintenance trial.[14] To address this feedback, the CADTH base cases applied an equal risk of URTIs, malignancies, and serious infections to all treatments. CADTH also considered a scenario analysis in which biologic-exposed patients on tofacitinib 10 mg twice daily in the maintenance phase had an increased *H. zoster* risk (to 5.0%) based on the OCTAVE Sustain trial.
- **Adverse event risks only applied in induction phase:** AE risks were only applied in the first cycle of the model due to a lack of longer-term data. This was deemed inappropriate given that AEs are likely to occur beyond treatment induction and the manufacturer's model would underestimate their impact, a contention that is supported by data from the OCTAVE Sustain trial.[14] To address this issue, the CADTH base cases applied the AE risks throughout all cycles, including the maintenance phase.

- **Treatment induction period length for tofacitinib may affect drug costs:** The product monograph for tofacitinib indicates tofacitinib should be discontinued in patients who show no evidence of adequate therapeutic benefit by week 16, while the manufacturer's base case assumes an induction period of eight weeks. A shorter induction period may underestimate the drug costs associated with tofacitinib, improving its cost-effectiveness relative to comparators. CADTH conducted a scenario analysis in which the induction period was extended to 16 weeks, as this may be a period used in clinical practice. The clinical expert consulted by CADTH indicated eight weeks should be sufficient to determine treatment response with tofacitinib, so this remained the induction period for tofacitinib in the CADTH base case reanalyses.
- **Manufacturer's analyses did not follow best practices:** The manufacturer's submitted model did not follow some of the CADTH guidelines for the economic evaluation of health technologies[12] or best practices, as detailed in the following:
  - The manufacturer's primary treatment population consisted of a mixed biologic-naive and biologic-exposed population, which is consistent with the approved indication and reimbursement request. Based on data from the clinical review, ITC and feedback from the clinical expert consulted by CADTH, these subgroups appear to have differing treatment efficacies. The CADTH base case was thus split into two subgroups, one analysis for biologic-naive patients and another for biologic-exposed patients.
  - The manufacturer's primary analysis was presented pairwise with tofacitinib relative to each comparator individually. Ideally this analysis should have been conducted sequentially, comparing a less-costly comparator with the next most-costly comparator in sequence, excluding dominated or extendedly dominated interventions, to identify the cost-effectiveness frontier. All CADTH reanalyses were conducted sequentially.
  - The model results for some of the presented analyses were unstable, which was likely due to using 1,000 iterations as opposed to a higher number of iterations at which results would be stable (e.g., 5,000). To address this issue, all CADTH reanalyses were conducted using 5,000 iterations.

CADTH Common Drug Review Reanalyses

CADTH undertook separate base-case analyses for biologic-naive and biologic-exposed patients, with the results reported in Table 7 and Table 8. The reanalyses addressed the identified limitations that could be modified within the manufacturer's model, as well as some minor issues with colectomy risk and conventional therapy mix, by:

- Applying a more appropriate utility value for post-colectomy (0.79 instead of 0.67)
- Applying equal AE risk for all URTIs, malignancies and infections (see Table 26 for values applied)
- Applying AE risk throughout all model cycles
- Applying a correction of 0.5120 to colectomy risk probabilities in accordance with the identification of a trend indicating lower probabilities of colectomy risk as patients are more recently diagnosed in the reference study (see Table 13 for information on the calculation of this value)
- Revising the distribution of conventional therapy for all comparators in model (the clinical expert consulted by CADTH indicated conventional therapy was underestimated).

Conventional therapy resource use for tofacitinib was based on concurrent therapy in the OCTAVE Sustain trial[14] to reflect that immunomodulators are not expected to be used in conjunction with tofacitinib [aminosalicylates = 72%, corticosteroids = 49%]; the distribution of conventional therapy for other treatments was revised to align with tofacitinib, although immunomodulator use (57%) was incorporated based on a previously published study.

Biologic-naive population

Based on the above revisions, the CADTH base case for the biologic-naive population determined the least costly comparator was continuing conventional UC therapy (Table 7). Infliximab biosimilar was the only non-dominated comparator, and the ICUR of infliximab biosimilar versus conventional UC therapy was $166,608 per QALY gained. Thus, if a decision-maker is unwilling to pay $166,608 per QALY, conventional UC therapy is the optimal therapy, whereas if they are willing to pay $166,608 per QALY, infliximab biosimilar is the optimal therapy. Tofacitinib had a 0% chance of being the preferred treatment up to a willingness-to-pay of $100,000 per QALY.

Table 7: Summary of Results of the CADTH Base-Case Analysis — Biologic-Naive

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$599,480	24.163		
Infliximab biosimilar	$627,137	24.329	$166,608	$166,608
Tofacitinib	$629,339	24.325	$184,315	Dominated by infliximab biosimilar
Adalimumab	$630,690	24.243	$390,125	Dominated by infliximab biosimilar
Golimumab	$633,985	24.286	$280,528	Dominated by infliximab biosimilar
Vedolizumab	$642,537	24.325	$265,784	Dominated by infliximab biosimilar
Infliximab	$648,760	24.329	$296,867	Dominated by infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Biologic-exposed patients

The CADTH base case for biologic-exposed patients found conventional UC therapy and tofacitinib to be the non-dominated therapies (Table 8). At a willingness-to-pay of up to $143,710 per QALY, continuing conventional UC therapy would be the optimal therapy, and if the willingness-to-pay was greater than $143,710 per QALY tofacitinib would be the optimal therapy. Tofacitinib had a 0% chance of being the preferred treatment up to a willingness-to-pay of $50,000 per QALY, but had 4% and 69% chances of being cost-effective at a willingness-to-pay of $100,000 and $200,000 per QALY, respectively.

Table 8: Summary of Results of the CADTH Base-Case Analysis — Biologic-Exposed

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$612,246	24.139		
Tofacitinib	$621,156	24.201	$143,710	$143,710
Infliximab biosimilar	$621,047	24.189	$176,020	Subject to extended dominance through conventional therapy and tofacitinib
Adalimumab	$620,639	24.169	$279,767	Subject to extended dominance through conventional therapy and tofacitinib, and conventional therapy and infliximab biosimilar
Golimumab	$621,876	24.179	$240,750	Dominated by infliximab biosimilar
Vedolizumab	$628,112	24.189	$317,320	Dominated by infliximab biosimilar
Infliximab	$630,947	24.189	$374,020	Dominated by infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

CADTH undertook a price-reduction analysis based on the manufacturer-submitted and CADTH base-case analyses, assuming proportional price reductions for tofacitinib. Using the manufacturer's base case, tofacitinib would be the optimal therapy at a willingness-to-pay of $50,000 per QALY with a price reduction of 60%.

In the CADTH base case for biologic-naive patients, if a price reduction of 80% were achieved, tofacitinib would be the optimal therapy at a willingness-to-pay between $39,932 and $7,061,000 per QALY. In this price-reduction scenario, infliximab biosimilar is still more effective than tofacitinib, but the price reduction for tofacitinib makes it cost-effective in comparison with infliximab biosimilar at a willingness-to-pay of $50,000 per QALY. For the biologic-exposed base case, if a price reduction of 50% were achieved, tofacitinib would be the optimal therapy at a willingness-to-pay greater than $36,415 per QALY. To reach an exact willingness-to-pay of $50,000 per QALY or lower in the biologic-exposed population, a price reduction of 44% would be required, while a price reduction of 74% would be required to reach this same willingness to pay in the biologic-naive population.

Table 9: CADTH Reanalysis Price-Reduction Scenarios

ICURs of Submitted Drug vs. Comparators			
Price	**Base-case analysis submitted by manufacturer**	**Reanalysis by CADTH — Biologic-naive**	**Reanalysis by CADTH — Biologic-exposed**
Submitted	If λ < $117,142 conventional therapy is optimal If $117,142 > λ > $148,615 infliximab biosimilar is optimal If λ > $148,615 tofacitinib is optimal	If λ < $166,608 conventional therapy is optimal If λ > $166,608 infliximab biosimilar is optimal Tofacitinib is dominated	If λ < $143,710 conventional therapy is optimal If λ > $143,710 tofacitinib is optimal
10% reduction	If λ < $106,620 conventional therapy is optimal If λ > $106,620 is optimal tofacitinib	If λ < $166,854 conventional therapy is optimal If $166,854 <λ < $271,417 tofacitinib is optimal If λ > $271,417 infliximab biosimilar is optimal	If λ < $123,807 conventional therapy is optimal If λ > $123,807 tofacitinib is optimal
20% reduction	If λ < $93,399 conventional therapy is optimal If λ > $93,399 tofacitinib is optimal	If λ < $148,270 conventional therapy is optimal If $148,270 <λ < $1,614,422 tofacitinib is optimal If λ > $1,614,422 infliximab biosimilar is optimal	If λ < $102,162 conventional therapy is optimal If λ > $102,162 tofacitinib is optimal
30% reduction	If λ < $80,741 conventional therapy is optimal If λ > $80,741 tofacitinib is optimal	If λ < $129,387 conventional therapy is optimal If $129,387<λ < $2,358,832 tofacitinib is optimal If λ > $2,358,832 infliximab biosimilar is optimal	If λ < $80,248 conventional therapy is optimal If λ > $80,248 tofacitinib is optimal
40% reduction	If λ < $68,227 conventional therapy is optimal If λ > $68,227 tofacitinib is optimal	If λ < $112,268 conventional therapy is optimal If $112,268<λ < $3,154,632 tofacitinib is optimal If λ > $3,154,632 infliximab biosimilar is optimal	If λ < $58,354 conventional therapy is optimal If λ > $58,354 tofacitinib is optimal
50% reduction	If λ < $55,233 conventional therapy is optimal If λ > $55,233 tofacitinib is optimal	If λ < $91,167 conventional therapy is optimal If $91,167 <λ < $3,536,286 tofacitinib is optimal If λ > $3,536,286 infliximab biosimilar is optimal	If λ < $36,415 conventional therapy is optimal If λ > $36,415 tofacitinib is optimal
60% reduction	If λ < $41,727 conventional therapy is optimal If λ > $41,727 tofacitinib is optimal	If λ < $76,167 conventional therapy is optimal If $76,167 <λ < $3,823,750 tofacitinib is optimal If λ > $3,823,750 infliximab biosimilar is optimal	NR
70% reduction	NR	If λ < $57,429 conventional therapy is optimal If $57,429 < λ < $6,100,667 tofacitinib is optimal If λ > $6,100,667 infliximab biosimilar is optimal	

ICURs of Submitted Drug vs. Comparators			
Price	**Base-case analysis submitted by manufacturer**	**Reanalysis by CADTH — Biologic-naive**	**Reanalysis by CADTH — Biologic-exposed**
80% reduction		If λ < $39,932 conventional therapy is optimal If $39,932 <λ < $7,061,000 tofacitinib is optimal If λ > $7,061,000 infliximab biosimilar is optimal	

λ = willingness-to-pay; ICUR = incremental cost-utility ratio; NR = not reported.

If the efficacy and safety of tofacitinib is assumed to be equivalent to the biologic comparators and used according to the product monograph dosing recommendations, the annual cost of tofacitinib is greater than the annual cost of at least one of the direct comparators based on publicly available prices (Table 10).

CADTH conducted a series of scenario analyses, which are reported in Appendix 3.

Issues for Consideration

- As noted by the clinical expert consulted by CADTH, there is the possibility for use of tofacitinib as an adjunct to primary biologic therapy given tofacitinib's fairly rapid action, which could help with breakthrough symptoms. This in turn may increase costs from tofacitinib if used off-label in conjunction with a biologic.
- The clinical expert consulted by CADTH also noted tofacitinib 10 mg twice daily may be continued in the maintenance phase in patients previously exposed to biologics, potentially increasing treatment-related costs with tofacitinib. The tofacitinib product monograph also states that "*depending on therapeutic response; 10 mg twice daily may also be used for maintenance in some patients.*"[2] A scenario analysis assessing the impact of tofacitinib 10 mg twice daily in the maintenance phase is presented in Appendix 3.
- There is the potential for increased nonadherence to tofacitinib when compared with biologics due to the oral mode of administration relative to the injectable and infusion mode of administration for biologics, based on feedback from the clinical expert consulted by CADTH. This may lead to decreased effectiveness from tofacitinib, thereby reducing its potential clinical benefit, although the impact of missing a dose(s) of tofacitinib compared with missing a dose(s) of other biologics is not known.
- Prophylactic *H. zoster* vaccine may be necessary, likely in conjunction with tofacitinib, according to the clinical expert consulted by CADTH. Additionally, there is a study currently underway listed at clinicaltrials.gov with an intervention of tofacitinib and a *H. zoster* vaccine. This may increase drug costs should prophylaxis for *H. zoster* be deemed necessary by clinicians prescribing tofacitinib, decreasing the cost-effectiveness of tofacitinib, as drug costs were a key driver in the model.
- The product monograph states that tofacitinib is not recommended to be used in combination with biological UC therapies or with potent immunosuppressants such as azathioprine and cyclosporine. This restriction was confirmed by the clinical expert consulted for this review. This restriction may affect members of the eligible patient population who are currently on immunosuppressants.

Patient Input

Patient input was received from the Gastrointestinal Society. The most important outcome for patients is sustained remission and or treatment response, which are the primary maintenance phase health states within the manufacturer's model. The patient input also noted that because patients sometimes stopped responding to their UC treatment, a variety of treatment options are important, which is a feature of the disease treatment pathway modelled in the manufacturer's submission, with subsequent treatment-switching upon loss of response to biologics or tofacitinib.

Conclusions

CADTH conducted reanalyses in the biologic-exposed and biologic-naive populations separately to address some of the key limitations. In the biologic-naive population, CADTH found that tofacitinib was more costly and less effective than infliximab biosimilar. Infliximab biosimilar remains more effective than tofacitinib in all price-reduction scenarios, but a price reduction of 74% for tofacitinib would make tofacitinib less costly and the ICUR for infliximab biosimilar compared with tofacitinib would increase to more than $50,000 per QALY.

In the biologic-exposed population, tofacitinib was found to be the optimal therapy at a willingness-to-pay above $143,710. When compared with conventional UC therapy, a price reduction of 44% would be required for tofacitinib to be cost-effective at a willingness-to-pay of $50,000 per QALY in the biologic-exposed population.

CADTH reanalyses could not address several important limitations, including those related to treatment efficacy and duration of treatment effect, and as such, the results of this economic evaluation should be viewed with caution.

Appendix 1: Cost Comparison

The comparators presented in Table 10 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table, which therefore may not represent the actual costs to public drug plans.

Table 10: CDR Cost Comparison Table for the Treatment of Ulcerative Colitis

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Cost per Month ($)	Average Cost per Year ($)
Tofacitinib (Xeljanz)	**5 mg 10 mg**	**Tab**	**23.9589[a] 42.3436[a]**	**10 mg twice daily for eight weeks, then 5 mg twice daily thereafter**	**Year 1: 1,625 Thereafter: 1,454**	**Year 1: 19,501 Thereafter: 17,442**
Comparators – Biologics						
Adalimumab (Humira)	40 mg/ 0.8 mL	Pre-filled syringe or auto-injector	769.9700	160 mg at week 0, 80 mg at week 2, and 40 mg every other week thereafter	Year 1: 1,989 Thereafter: 1,668	Year 1: 23,869 Thereafter: 20,019
Golimumab (Simponi)	50 mg/ 0.5 mL 100 mg/ 1 mL	Pre-filled syringe or auto-injector	1555.5000[b] 1556.0000[b]	200 mg at week 0, 100 mg at week 2, and 50 mg every four weeks	Year 1: 2,009 Thereafter: 1,685	Year 1: 24,112 Thereafter: 20,222
Infliximab (Inflectra)	100 mg/ vial	Lyophilized powder for reconstitution	525.0000	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter	Year 1: 1,531 Thereafter: 1,138	Year 1: 18,375 Thereafter: 13,650
Infliximab (Remicade)	100 mg/ vial	Lyophilized powder for reconstitution	977.0000[b]	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter	Year 1: 2,850 Thereafter: 2,117	Year 1: 34,195 Thereafter: 25,402
Vedolizumab (Entyvio)	300 mg	Powder for concentrate for solution for infusion	3291.0000[b]	300 mg by IV at week 0, 2, and 6, then every 8 weeks thereafter	Year 1: 2,400 Thereafter: 1,783	Year 1: 28,796 Thereafter: 21,392
Comparators – Aminosalicylates						
5-ASA (Asacol, Asacol 800)	400 mg 800 mg	Tab Ent. tab	0.3951 1.1358	4.8 g daily in divided doses	144 207	1,731 2,487
5-ASA (Mesasal)	500 mg	Ent. tab	0.6559	Active: 1.5 g to 3 g tabs daily in divided doses Maint: 1.5 g daily in divided doses	60 to 120 60	718 to 1,436 718

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Cost per Month ($)	Average Cost per Year ($)
5-ASA (Mesavant)	1.2 g	Tab	1.7079	Active: 2 to 4 tabs once daily Maint: 1 to 2 tabs once daily	104–208 52 to 104	1,247 to 2,494 623 to 1,247
5-ASA (Pentasa)	500 mg	Delayed-release tab	0.5743	2 g to 4 g daily in divided doses	70 to 140	838 to 1,677
	1g 1g/100mL 4g/100mL	Supp Enema Enema	1.1485 4.4770 5.6419	Sup: 1 g daily Enema: 1 g to 4 g daily	35 136 to 172	419 1,634 to 2,059
5-ASA (Salofalk)	500 mg	Ent. tab	0.6294	3 g to 4 g daily in divided doses	115	1,378
	500 mg 1000 mg	Supp Supp	1.4050 2.0637	Sup: 1 g to 1.5 g daily	63 to 128	753 to 1,538
	2g/1000 mL 4g/1000 mL	Rect susp	4.4000[b] 7.4643	Active: 4 g nightly Maint: 2 g nightly or 4 g every two nights	227 114 to 134	2,724 1,362 to 1,606
Olsalazine (Dipentum)	250 mg	Cap	0.5330	Active: 1 g to 3 g daily in divided doses Maint: 1 g daily in divided doses	65 to 195 65	778 to 2,335 778
Sulfasalazine (Salazopyrin, generics)	500 mg	Tab	0.1804	Active: 1 g to 2 g three to four times daily Maint: 1 g two to three times daily	33 to 88 22-33	395 to 1,054 263 to 395
Comparators – Corticosteroids						
Betamethasone enema (Betnesol)	5mg/ 100mL	Enema	11.8214	5 mg nightly	360	4,315
Budesonide (Entocort)	3 mg	Cap	1.8110[b]	3 mg three times per day up to eight weeks, followed by 6 mg daily for up to 3 months	51	608
Hydrocortisone enema (Cortenema) (Cortifoam)	100 mg/ 60 mL 15 g/pack (14 doses)	Enema Rect. Aerosol	7.5729 107.2200	60 mL nightly or every other night One dose nightly or every other night	115 to 230 116 to 233	1,382 to 2,764 1,398 to 2,795
Hydrocortisone (Solu-cortef)	100 mg 250 mg	Vial	4.0500[b] 7.0300[b]	100 mg to 500 mg IV daily to induce remission; then switch to other agent	122 to 420	Daily cost: 4 to 14
Prednisone (generic)	1 mg 5 mg 50 mg	Tab	0.1095[b] 0.0220 0.1735	40 mg to 60 mg daily to induce remission; then lower dose	0.18 to 0.22	64 to 79 or lower

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Cost per Month ($)	Average Cost per Year ($)
Comparators – Immunomodulators						
Azathioprine (Imuran and generic)	50 mg	Tab	0.2405	up to 2.5 mg/kg daily	22	263
Mercaptopurine (Purinethol and generic)	50 mg	Tab	2.8610	1.5 to 2.5 mg/kg daily	174 to 261	2,089 to 3,133
Methotrexate (generic)	2.5 mg	Tab	0.6325	10–25 mg once a week	11 to 27	132 to 329

ASA = aminosalicylate; cap = capsule; CDR = CADTH Common Drug Review; ent = enteric; IV = intravenous; maint = maintenance; sol inj = solution for injection; supp = suppository; tab = tablet.

Note: All weight-based calculations assume a weight of 73.6 kg, taken from the manufacturer's baseline patient characteristics, and assume wastage.

[a] Based on manufacturer's submission.[1]

[b] Price obtained from Saskatchewan Drug Benefit (July 17, 2018).

Source: Ontario Drug Benefit/Comparative Drug Index (effective from July 17, 2018) unless otherwise noted. Annual period assumes 52 weeks, 365 days.

Appendix 2: Additional Information

Table 11: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	The manufacturer's economic model results lacked consistency and did not follow best practice in several areas (see Limitations). The model was difficult to follow, despite the (limited) Markov traces that the manufacturer provided, and anomalous results were detected that limited CADTH's confidence in the model results.		
Was the material included (content) sufficient?		X	
Comments	The manufacturer provided a revised model with Markov traces upon request, although these were limited in their scope.		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

Table 12: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

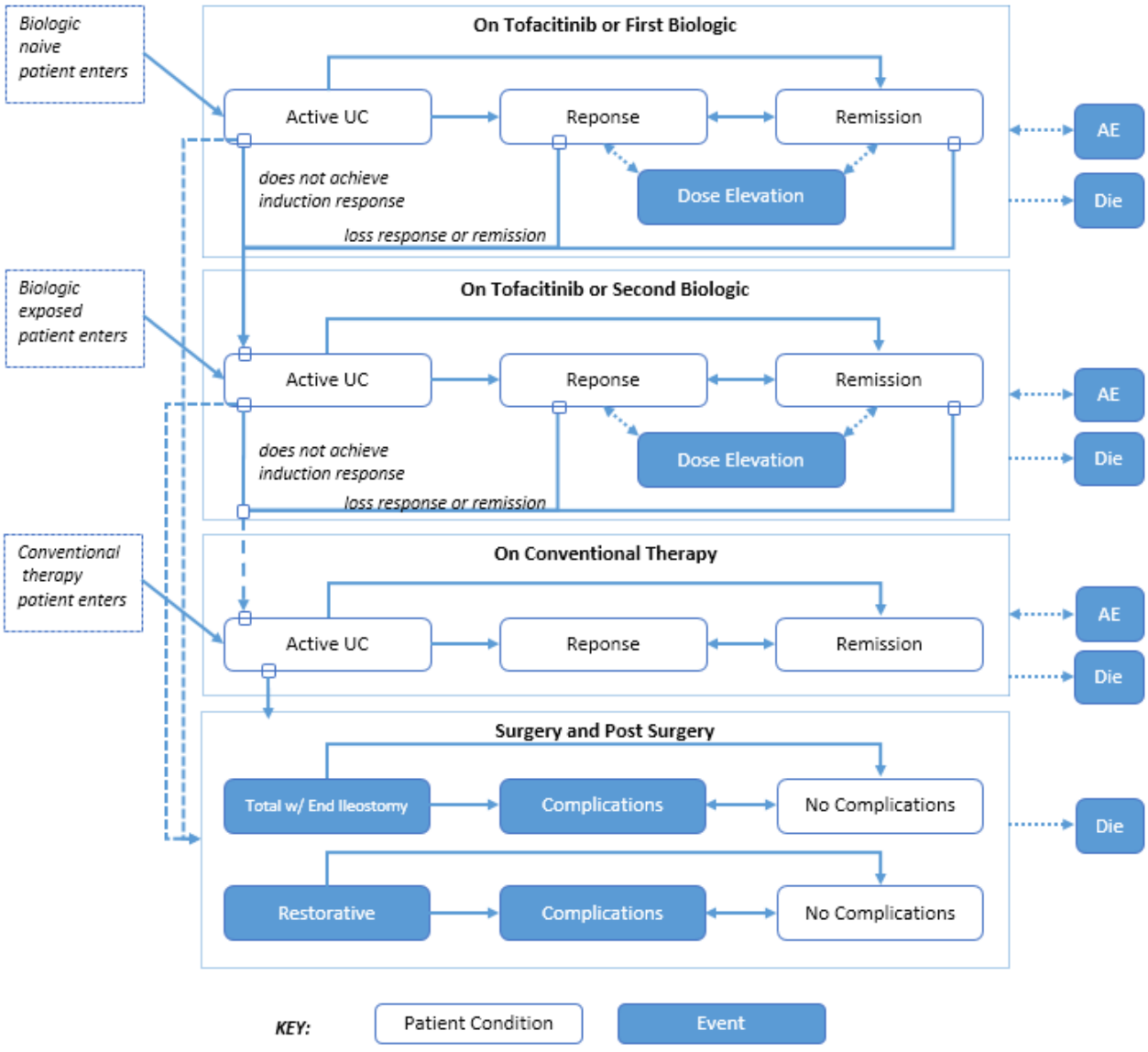
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

CDR = CADTH Common Drug Review.

Appendix 3: Reviewer Worksheets

Manufacturer's Model Structure

Figure 1: Manufacturer's Model Structure



AE = adverse event; UC = ulcerative colitis.
Source: Manufacturer's pharmacoeconomic submission.[1]

Table 13: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	Information on previous biologic exposure, mean age, proportion of each sex, average weight and time since diagnosis obtained from the combined tofacitinib 10 mg arms from OCTAVE Induction 1 and 2.[15]	Appropriate.
Efficacy	ITC submitted by the manufacturer was used to estimate the relative efficacy of tofacitinib for response and clinical remission in both treatment-exposed and -naive populations.	There are concerns with the methods used in the treat-through analysis, as they relied on imputed data for tofacitinib and golimumab to conduct the analysis. The imputation method required separating patients into subgroups based on their response to induction treatment and thus randomization was not maintained. Additionally, while some of the imputation methods used had been published, the CADTH appraisal of the ITC noted that other imputation methods were developed by the ITC authors with some arbitrary assumptions, and that none of the imputation methods have been validated.
Natural history	Risk of colectomy for patients not responding to treatment obtained from the University of Manitoba Inflammatory Bowel Disease Epidemiology Database.[5] Distribution of colectomy type and long-term complications from colectomy obtained from Loftus et al. (2008).[16] Risk of early complications from colectomy from Causey et al. (2013).[17]	Acceptable source. The probabilities published by Targownik et al. were generated from patients diagnosed as far back as 1987. The author identified a temporal (secular) trend with lower probabilities of colectomy as a patient has been diagnosed more recently. This temporal trend was quantified with a hazard ratio of 0.96 for each year diagnosed after 1987. As the maintenance trial for tofacitinib was started in 2012 and patients had been diagnosed for an average of 8.6 years, 16.4 years had elapsed since 1987 (2012 (year trial started)-8.6 (average length since diagnosis from maintenance trial)-1987 (year of study)=16.4 years elapsed since 1987). The correction to be applied to each probability would be 0.96^16.4 or 0.5120. This has been applied in the CADTH base cases. Acceptable. Acceptable.

Data Input	Description of Data Source	Comment
Utilities	For induction-phase health states of clinical remission, response without remission, and no response, utilities were derived from the OCTAVE 1 and 2 trials, while maintenance phase values for these same health states were derived from the OCTAVE Sustain trial.[15]	Acceptable. These values were based on a post hoc analysis using the EQ-5D index, although the tariff used is unknown.
	Post-colectomy utility value was obtained from the CADTH pharmacoeconomic submission for golimumab in 2014.[18]	Not appropriate. In the model, patients with active UC are expected to have a higher utility than patients post-colectomy. This assumption does not meet face validity, as patients with active UC would be expected to have as bad, if not worse, utility than someone who has had a colectomy. We have identified a value in the literature that is more appropriate (0.79 vs. 0.67) and was elicited using the same scale as the other utility values used within the model, the EQ-5D index.[13] Additionally, no disutilities were applied post-colectomy for adverse events, meaning patients who experienced colectomy with complications had the same utility as those without complications. The manufacturer justified this choice based on the assumption that the post-colectomy utility value obtained from the literature likely already accounted for complications. This does not appear to be appropriate, given patients with no complications are anticipated to have a higher utility than patients with complications.
	Adverse event disutilities were obtained from the vedolizumab submission to NICE in 2016 for all AEs except URTI, which was based on an assumption that it was the same as tuberculosis, and *Herpes zoster*, which was taken from Drolet et al.[7]	Appropriate.
Adverse events (serious infections, upper respiratory tract infection, tuberculosis, malignancies, acute infusion AEs, injection-site reactions, *Herpes zoster*)	All potential AEs listed in the model were based on a previous health economic model of biologics for the treatment of UC submitted to NICE.[19]	Treatment discontinuation due to AEs was not modelled due to a lack of data on such events from the tofacitinib RCTs.
	Actual risk inputs for each AE were derived from the ITT populations from each of the induction and maintenance phases of trials for each treatment.	Not acceptable. The AE risks were derived from trials not powered for safety outcomes and had the primary objective of determining treatment efficacy. None of the safety inputs appeared to be adjusted for baseline risk of AE in the placebo/control groups. It is also important to note that tofacitinib is the only medication that is associated with a risk of *Herpes zoster* based on the manufacturer's model inputs. This risk increases based on dose and over time. To address this increased risk, the risk *of H. zoster* associated with tofacitinib 10 mg twice daily in the maintenance phase of treatment was applied to the CDR base case for biologic exposes patients.

Data Input	Description of Data Source	Comment
		No AE natural history was modelled probabilistically.
Mortality	Based on WHO life tables.[6]	May be acceptable, although Canadian sources are preferred.
Resource use and costs		
Drug	Dosing regimens were based on product monographs, all unit costs obtained from Ontario Drug Benefit Formulary.[11]	Drug costs for conventional therapies were based on the average distribution of all concomitant conventional therapies across all clinical trials included in the ITC. This was deemed appropriate by the clinical expert consulted by CADTH given that there is no specific recommended regimen for conventional UC therapy and treatment selection varies from patient to patient, though the total amount of conventional therapy was indicated to be underestimated. CADTH considered data from the OCTAVE trials and published literature.
Administration	Administration costs obtained from the Ministry of Health and Long-Term Care (MOHLTC) Schedule of Benefits.[10]	Acceptable.
AEs	Costs from AEs related to medication use were obtained from the Ontario Case Costing Initiative (OCCI),[9] while colectomy AE costs were obtained from the MOHLTC Schedule of Benefits.[10]	Source acceptable. Not modelled probabilistically.
Health state	Resource use by treatment response was obtained predominantly from Tsai et al.,[8] as was post-colectomy medical resource use. Costs for medical resources were obtained from the OCCI [9] and MOHLTC Schedule of Benefits.[10]	Appropriate. Risks of subsequent procedures and their costs following colectomy were included in the initial colectomy event. Costs post-colectomy not modelled probabilistically.

AE = adverse event; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions questionnaire; ITC = indirect treatment comparison; ITT = intention-to-treat; OCCI = Ontario Case Costing Initiative; MOHLTC = Ministry of Health and Long-Term Care; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; UC = ulcerative colitis; URTI = upper respiratory tract infection; WHO = World Health Organization.

Table 14: Manufacturer's Key Assumptions

Assumption	Comment
Assessment of response to treatment induction at 8 weeks.	Appropriate. Deemed by the clinical expert consulted by CADTH to be an acceptable amount of time for assessment of treatment response. The manufacturer did acknowledge that comparator studies used a period of 8 to 12 weeks for assessment of response to treatment.
Patients who did not respond to tofacitinib or biologic treatment switched to a subsequent biologic or conventional therapy at 8 weeks.	May be appropriate, due to the impact of the inclusion of the second line of therapy on the results and associated uncertainty. While CADTH would like to have excluded this from the base case, CADTH identified anomalous results when removing second-line treatments and had to leave this in the base case. Additionally, the product monograph notes that up to 16 weeks may be used to assess the response to tofacitinib.
Biologic-naive patients failing tofacitinib or biologic treatment subsequently received vedolizumab, except for patients starting on vedolizumab, who received infliximab.	Inappropriate, as this may bias against vedolizumab due to a different second-line treatment efficacy. Additionally, there is no clear preference among clinicians for second-line treatments based on feedback from the clinical experts consulted by CADTH.
Patients on conventional therapy alone were assumed to continue receiving conventional therapy until colectomy or death, irrespective of response.	Appropriate for patients who have already exhausted other treatment options, although patients are likely to alternate between different therapies. Not appropriate for patients starting on conventional therapy who were biologic-naive. Guidelines state that patients not responding to conventional therapy should switch to a biologic agent.
Probability of response and remission at 52 weeks remained constant beyond that time point.	Not appropriate. Based on feedback obtained from the clinical experts consulted by CADTH, some treatment waning is likely, although it is uncertain if such waning would be different for tofacitinib compared with other treatments.
AE probabilities, costs and disutilities applied at one-time point only.	Adverse events may occur beyond the eight-week induction period, although the manufacturer did not include them in the model beyond this period due to a lack of long-term data. This should have been included in the model.
Treatment discontinuation not included in model; patients continue to receive treatment as long as they continue to respond.	It is unclear whether differential treatment discontinuation between tofacitinib and other UC treatments would be observed.
Costs of conventional therapy based on average distribution of all conventional therapy medications from comparator trials.	Not appropriate. Patients on tofacitinib would not be taking immunomodulators, while the distribution of CT for all other treatments was underestimated, based on feedback from the clinical expert consulted by CADTH.
Only patients with active UC were at risk of colectomy.	Appropriate. The clinical expert consulted by CADTH indicated that colectomy should only be used in patients not achieving an adequate treatment response with available pharmacologic options.
Subcutaneous drugs were assumed to be self-administered 90% of time, and in those cases there was a one-time training cost.	Appropriate.
Patients are expected to have a higher utility with active UC than post-colectomy.	Not appropriate as it does not meet face validity. Previous models accepted by CDR had a higher utility value post-colectomy than for active UC.

AE = adverse event; CDR = CADTH Common Drug Review; CT = conventional therapy; UC = ulcerative colitis.

Manufacturer's Results

The manufacturer conducted pairwise comparisons on the subgroups. The results are presented in Table 15 and Table 16.

Biologic-Naive Subgroup

Table 15: Summary of Results of the Manufacturer's Base Case – Biologic-Naive

	Total Costs ($)	Incremental Cost of Tofacitinib ($)	Total QALYs	Incremental QALYs of Tofacitinib	Incremental Cost per QALY
Tofacitinib	$613,063		23.898		
Adalimumab	$612,912	$151	23.784	0.115	$1,312
Conventional UC therapy	$582,289	$30,773	23.658	0.240	$128,061
Golimumab	$615,765	−$2,702	23.784	0.056	Dominant
Infliximab biosimilar	$609,325	$3,738	23.895	0.003	$1,101,156
Infliximab	$630,844	−$17,781	23.896	0.002	Dominant
Vedolizumab	$626,134	−$13,072	23.882	0.017	Dominant

QALY = quality-adjusted life-year; UC = ulcerative colitis.

Source: Manufacturer's pharmacoeconomic submission.[1]

Biologic-Exposed Subgroup

Table 16: Summary of Results of the Manufacturer's Base Case – Biologic-Exposed

	Total Costs ($)	Incremental Cost of Tofacitinib ($)	Total QALYs	Incremental QALYs of Tofacitinib	Incremental Cost per QALY
Tofacitinib	$593,813		23.714		
Adalimumab	$592,579	$1,234	23.664	0.050	$24,843
Conventional UC therapy	$584,333	$9,480	23.618	0.096	$98,625
Golimumab	$593,762	$51	23.677	0.037	$1,388
Infliximab biosimilar	$593,400	$413	23.686	0.028	$14,622
Infliximab	$603,318	-$9,505	23.676	0.028	Dominant
Vedolizumab	$600,470	-$6,657	23.689	0.025	Dominant

QALY = quality-adjusted life-year; UC = ulcerative colitis.

Source: Manufacturer's pharmacoeconomic submission.[1]

Scenario Analyses

The manufacturer conducted a number of scenario analyses to evaluate the effects of varying certain model assumptions. The results of these scenario analyses are presented in Table 17. The largest impact on the manufacturers base-case results was assuming increased doses for patients on infliximab, adalimumab, and vedolizumab improved the cost-effectiveness of tofacitinib; extending the induction phase from 8 weeks to 16 weeks, and increasing the tofacitinib dose to 10 mg twice daily in biologic-exposed patients resulted in golimumab no longer being dominated by tofacitinib. These results were not reported based on biologic-naive and biologic-exposed subgroups.

Table 17: Manufacturer's Scenario Analysis Results

Parameter	Description of Scenario	ICUR (Tofacitinib vs. Comparators)					
		Vedolizumab	Infliximab	Infliximab Biosimilar	Adalimumab	Golimumab	Conventional Therapy
No changes	**Manufacturer base case**	Tofacitinib dominant	Tofacitinib dominant	$145,184	$8,897	Tofacitinib dominant	$118,387
Dose optimization	Dose optimization assumption: dosage doubled in 29% of patients on infliximab and 13% of patients on adalimumab, vedolizumab, and golimumab)	Tofacitinib dominant	Tofacitinib dominant	Tofacitinib dominant	Tofacitinib dominant	Tofacitinib dominant	$138,347
Efficacy assumption for infliximab and golimumab in biologic-exposed patients	Efficacy for infliximab and golimumab in biologic-exposed patients based on the difference between tofacitinib and infliximab and golimumab in biologic-naive patients	Tofacitinib dominant	Tofacitinib dominant	$782,782	$9,376	Tofacitinib dominant	$118,048
Extended induction phase for nonresponders on tofacitinib	Patients on tofacitinib who do not respond after the 8-week induction phase continue on induction treatment for an additional 8 weeks	Tofacitinib dominant	Tofacitinib dominant	$84,222	$36,219	$29,105	$107,389
Tofacitinib maintenance dosage for biologic-exposed	Tofacitinib dosage of 10 mg in maintenance therapy is active for biologic-exposed patients only	Tofacitinib dominant	Tofacitinib dominant	$233,886	$64,215	$67,245	$138,146
Colectomy risk	Risk of colectomy remains constant based on previously published models	Tofacitinib dominant	Tofacitinib dominant	$154,835	$13,340	Tofacitinib dominant	$108,923
Self-administration of SC Treatments	Assume all patients self-administer	Tofacitinib dominant	Tofacitinib dominant	$129,284	$9,371	Tofacitinib dominant	$118,877
Utility by health state	Source of utility from vedolizumab NICE submission[20]	Tofacitinib dominant	Tofacitinib dominant	$141,404	$8,099	Tofacitinib dominant	$96,849

Parameter	Description of Scenario	ICUR (Tofacitinib vs. Comparators)					
		Vedolizumab	Infliximab	Infliximab Biosimilar	Adalimumab	Golimumab	Conventional Therapy
	Source of utility from Tsai et al. (2008)[8]	Tofacitinib dominant	Tofacitinib dominant	$159,726	$4,410	Tofacitinib dominant	$58,639
	Source of utility from Woehl et al. (2007)[21]	Tofacitinib dominant	Tofacitinib dominant	$138,094	$5,179	Tofacitinib dominant	$66,100
	Source of utility from Swinburn et al. (2012)[22]	Tofacitinib dominant	Tofacitinib dominant	$135,412	$5,444	Tofacitinib dominant	$64,732

ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; SC = subcutaneous.

Source: Manufacturer's pharmacoeconomic submission.[1]

The manufacturer also conducted several sensitivity analyses to identify key model drivers and the robustness of model conclusions. The analyses assessed varying the time horizon to 10 years (from lifetime), increasing and decreasing the cost and utility discount rate, varying the efficacy of tofacitinib and its competitors based on upper- and lower-bound values (separately), altering the risks of adverse events, altering risk of colectomy, and varying the amount of resource use, costs and utilities by using their upper- and lower-bound values. The manufacturer identified the model time horizon, cost and utility discounting, treatment efficacy, and utility following colectomy as key drivers in the model.

CADTH Common Drug Review Reanalyses

Several scenario analyses were undertaken to consider alternate scenarios from those in the CADTH base case analyses:

1. Tofacitinib dosing was altered in the maintenance phase, as it is uncertain what dosing will be used in the maintenance phase by clinicians. Only dosing for patients in the biologic-exposed patients could be altered, thus the impact of this assumption could not be assessed in the biologic-naive population. In this scenario, tofacitinib 10 mg twice daily in the maintenance phase was assumed for biologic-exposed patients, as well as a higher rate of *Herpes zoster* (5%), which was seen in the OCTAVE Sustain maintenance trial and was applied over the maintenance phase.
    a. Price-reduction scenarios with this assumption were also conducted.
2. Conventional therapy distribution based on manufacturer's assumptions
    a. biologic-naive patients
    b. biologic-exposed patients
3. Extending tofacitinib induction period to 16 weeks
    a. biologic-naive patients
    b. biologic-exposed patients

Table 18: Results of CADTH Scenario Analysis 1 – Biologic-Exposed Patients

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$602,501	24.136		
Infliximab biosimilar	$611,236	24.186	$174,700	$174,700
Tofacitinib	$622,911	24.208	$283,472	$530,682
Adalimumab	$610,871	24.166	$279,000	Subject to extended dominance through conventional UC therapy and infliximab biosimilar
Golimumab	$621,076	24.176	$464,375	Dominated by infliximab biosimilar
Vedolizumab	$618,293	24.185	$322,286	Dominated by infliximab biosimilar
Infliximab	$621,137	24.186	$372,720	Dominated by infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Table 19: Results of CADTH Price Reduction Analysis for Scenario Analysis 1

ICURs of Submitted Drug vs. Comparator	
Price	**Reanalysis by CADTH – Biologic-exposed**
Submitted	If λ < $174,700 conventional UC therapy is optimal If $174,700 < λ < $530,682 infliximab biosimilar is optimal If λ > $530,682 tofacitinib is optimal
10% reduction	If λ < $174,535 conventional UC therapy is optimal If $174,535 < λ < $418,598 infliximab biosimilar is optimal If λ > $418,598 tofacitinib is optimal
20% reduction	If λ < $173,347 conventional UC therapy is optimal If $173,347 < λ < $298,329 infliximab biosimilar is optimal If λ > $298,329 tofacitinib is optimal
30% reduction	If λ < $175,140 conventional UC therapy is optimal If $175,140 < λ < $177,254 infliximab biosimilar is optimal If λ > $177,254 tofacitinib is optimal
40% reduction	If λ < $138,843 conventional UC therapy is optimal If λ > $138,843 tofacitinib is optimal
50% reduction	If λ < $103,795 conventional UC therapy is optimal If λ > $103,795 tofacitinib is optimal
60% reduction	If λ < $67,538 conventional UC therapy is optimal If λ > $67,538 tofacitinib is optimal
70% reduction	If λ < $32,071 conventional UC therapy is optimal If λ > $32,071 tofacitinib is optimal

λ = willingness-to-pay; ICUR = incremental cost-utility ratio; UC = ulcerative coliltis.

Table 20: Results of CADTH Scenario Analysis 2a – Biologic-Naive Patients

	Total Costs ($)	Total QALYs	Incremental cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$582,562	24.170		
Infliximab biosimilar	$610,006	24.335	$166,327	$166,327
Tofacitinib	$613,867	24.332	$193,241	Dominated by infliximab biosimilar
Adalimumab	$614,656	24.250	$401,175	Dominated by infliximab biosimilar
Golimumab	$617,908	24.293	$287,366	Dominated by infliximab biosimilar
Vedolizumab	$625,389	24.331	$266,006	Dominated by infliximab biosimilar
Infliximab	$632,551	24.335	$302,964	Dominated by infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Table 21: Results of CADTH Scenario Analysis 2b – Biologic-Exposed Patients

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$586,105	24.125		
Tofacitinib	$595,363	24.187	$149,323	$149,323
Infliximab biosimilar	$594,764	24.175	$173,180	Subject to extended dominance through conventional UC therapy and tofacitinib
Adalimumab	$594,433	24.155	$277,600	Subject to extended dominance through conventional UC therapy and tofacitinib
Golimumab	$595,629	24.165	$238,100	Dominated by infliximab biosimilar
Vedolizumab	$601,768	24.174	$319,653	Dominated by infliximab biosimilar
Infliximab	$604,654	24.175	$370,980	Dominated by tofacitinib

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Table 22: Results of CADTH Scenario Analysis 3a – Biologic-Naive Patients

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$598,963	24.168		
Tofacitinib	$634,024	24.396	$153,776	$153,776
Infliximab biosimilar	$626,623	24.334	$166,627	Subject to extended dominance through conventional UC therapy and tofacitinib
Adalimumab	$630,191	24.249	$385,531	Dominated by infliximab biosimilar
Golimumab	$633,500	24.292	$278,524	Dominated by infliximab biosimilar
Vedolizumab	$642,016	24.330	$265,759	Dominated by infliximab biosimilar
Infliximab	$648,229	24.334	$296,783	Dominated by infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Table 23: Results of CADTH Scenario Analysis 3b – Biologic-Exposed Patients

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$601,556	24.128		
Tofacitinib	$614,014	24.210	$601,556	$151,927
Infliximab biosimilar	$610,300	24.178	$614,014	Subject to extended dominance through conventional UC therapy and tofacitinib
Adalimumab	$609,925	24.158	$610,300	Subject to extended dominance through conventional UC therapy and tofacitinib
Golimumab	$611,114	24.168	$609,925	Dominated by infliximab biosimilar
Vedolizumab	$617,348	24.177	$611,114	Dominated by infliximab biosimilar
Infliximab	$620,210	24.178	$617,348	Dominated by infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Additionally, two exploratory analyses were conducted:

- Mixed biologic-exposed and biologic-naive population, with tofacitinib 10 mg twice daily in maintenance phase for biologic-exposed patients
- Mixed biologic-exposed and biologic-naive population, with tofacitinib 5 mg twice daily in maintenance phase for biologic-exposed patients.

All analyses were conducted using 5,000 iterations as recommended by the CADTH guidelines for the economic evaluation of health technologies.[12]

Table 24: Results of CADTH Exploratory Analysis 1

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$600,810	24.147		
Infliximab biosimilar	$618,272	24.250	$169,534	$169,534
Tofacitinib	$624,929	24.267	$200,992	$391,588
Adalimumab	$619,710	24.200	$356,604	Dominated by infliximab biosimilar
Golimumab	$621,895	24.226	$266,899	Dominated by infliximab biosimilar
Vedolizumab	$629,134	24.248	$280,436	Dominated by infliximab biosimilar and tofacitinib
Infliximab	$633,572	24.250	$318,078	Dominated by infliximab biosimilar and tofacitinib

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Table 25: Results of CADTH Exploratory Analysis 2

	Total Costs ($)	Total QALYs	Incremental Cost per QALY	
			Versus Conventional Therapy	Sequential ICUR
Conventional UC therapy	$601,639	24.153		
Infliximab biosimilar	$619,082	24.257	$167,721	$167,721
Tofacitinib	$620,295	24.262	$171,156	$242,600
Adalimumab	$620,534	24.207	$349,907	Dominated by tofacitinib and infliximab biosimilar
Golimumab	$622,695	24.232	$266,532	Dominated by tofacitinib and infliximab biosimilar
Vedolizumab	$629,945	24.254	$280,257	Dominated by tofacitinib and infliximab biosimilar
Infliximab	$634,367	24.256	$317,748	Dominated by tofacitinib and infliximab biosimilar

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; UC = ulcerative colitis.

Table 26: Adverse Event Risks Used Within the CADTH Common Drug Review Reanalyses

	Serious infection	URTI	Tuberculosis	Malignancies	Acute infusional AE	Injection site reaction	*Herpes zoster*
Adalimumab	0.00%	NR	0.28%	0.00%	NR	7.36%	0.00%
Conventional UC therapy	0.00%	0.00%	0.00%	0.00%	NR	0.23%	0.00%
Golimumab	0.00%	0.00%	0.47%	NR	2.35%	3.91%	0.00%
Infliximab biosimilar	0.00%	0.00%	NR	NR	8.29%	NR	0.00%
Infliximab	0.00%	0.00%	NR	NR	8.29%	NR	0.00%
Tofacitinib	0.00%	0.00%	0.00%	0.00%	NR	0.00%	1.30%
Vedolizumab	0.00%	0.00%	NR	0.00%	3.51%	NR	0.00%

AE = adverse event; UC = ulcerative colitis; URTI = upper respiratory tract infection.

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