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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Report

VEDOLIZUMAB (ENTYVIO SC)

Takeda Canada Inc.

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab, a tumor necrosis factor-alpha antagonist.

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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.

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Abbreviations

CDEC	CADTH Canadian Drug Expert Committee
ICER	incremental cost-effectiveness ratio
NMA	network meta-analysis
QALY	quality-adjusted life-year
SC	subcutaneous
TNF	tumour necrosis factor
UC	ulcerative colitis
WTP	willingness to pay

Executive Summary

The executive summary comprises two tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Vedolizumab (Entyvio SC) ,108 mg/0.68 mL single-use pre-filled syringe or pen
Submitted price	Vedolizumab, 108 mg/0.68 mL,SC injection: $822.50 per pre-filled syringe or pen
Indication	For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	April 7, 2020
Reimbursement request	As per indication
Sponsor	Takeda Canada Inc.
Submission history	Previously reviewed: Yes Ulcerative colitis (reviewed for IV formulation): • Indication: Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist. • Recommendation date: October 28, 2015 • Recommendation: Reimburse with clinical criteria and/or conditions Crohn's disease (reviewed for IV formulation): • Indication: Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist, or who have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids. • Recommendation date: October 27, 2016 • Recommendation: Reimburse with clinical criteria and/or conditions

NOC = Notice of Compliance; SC = subcutaneous; TNF = tumour necrosis factor.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree (induction phase) and Markov cohort model (maintenance phase)
Target population	Patients (≥ 18 years of age) with moderately to severely active UC with an inadequate response to conventional therapy or anti–TNF alpha (i.e., anti–TNF alpha naive or anti–TNF alpha exposed)
Treatment	Vedolizumab SC
Comparators	• Vedolizumab IV (Entyvio IV) • Adalimumab (Humira) • Infliximab biosimilar (Renflexis) • Golimumab (Simponi) • Continuing conventional therapy (mesalazine, azathioprine, and prednisolone)
Perspective	Canadian publicly funded health care payer
Outcome(s)	QALYs
Time horizon	Lifetime (63 years)
Key data source	Sponsor-conducted NMA
Submitted results for base case	According to the deterministic sequential analysis, the incremental ICER of vedolizumab SC versus conventional therapy was $100,582 per QALY gained.
Key limitations	• Comparative treatment efficacy informed by the sponsor's NMA is uncertain due to a lack of transparency in the systematic review and the limited size of the evidence base that resulted in imprecision in the effect estimates. The CADTH Clinical Review Report noted heterogeneity in the trial designs and patient populations that was not addressed within the sponsor's analysis. • Given the wide credible intervals in the relative treatment effects estimated from the NMA and the arbitrary definitions of parameter uncertainty, the sponsor's probabilistic ICERs were unstable. In each probabilistic run of the economic model, the resulting ICERs were substantially different, making it difficult to draw conclusions. • Ustekinumab and tofacitinib are relevant comparators that were excluded from the sponsor's base-case analysis. • Some surgery-related probabilities (e.g., probability of receiving surgery in active UC patients and the probability of surgery-related complications) were overestimated, introducing bias into the model. • Surgery-related costs (including post-surgery complications) were calculated incorrectly, resulting in overestimation. • Resource use was not reflective of Canadian clinical practice, according to the clinical expert consulted by CADTH. • Limited reporting in the trials included within the sponsor's NMA may have introduced uncertainty as to whether parameters on dose escalation and the loss and regaining of response within the economic model were informed by the available clinical evidence. There were further inconsistencies between the dose escalation stated within the respective product monographs and the dose escalation applied in the model.

Component	Description
CADTH reanalysis results	CADTH conducted deterministic reanalyses separately for anti–TNF alpha naive and anti–TNF alpha exposed patients. CADTH further revised the sponsor's economic analysis by: • including ustekinumab and tofacitinib as comparators • using alternate data to inform the probability of surgery and the probability of post-surgery complications • treating surgery and post-surgery complications as one-time costs • amending resource use to reflect Canadian clinical practice • removing dose escalation and the loss and regaining of response. The sequential ICERs of the CADTH reanalyses were as follows: • anti–TNF alpha naive population: • tofacitinib versus conventional therapy: $91,883 per QALY gained • anti–TNF alpha exposed population: • tofacitinib versus conventional therapy: $117,761 per QALY gained • Vedolizumab SC versus tofacitinib: $1,152,959 per QALY gained. [redacted]. CADTH could not address the limitations associated with the sponsor's NMA and, given the uncertainty and limited transparency associated with the sponsor's NMA, the results of the economic analysis should be interpreted with caution.

ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; QALY= quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis.

Conclusions

Given issues with the stability of the sponsor's probabilistic analysis (i.e., wide variation in the incremental cost-effectiveness ratios [ICERs] at each model run due in part to the wide credible intervals within the sponsor's submitted network meta-analysis [NMA]), CADTH conducted reanalyses deterministically for both the anti–tumour necrosis factor (TNF) alpha naive populations and anti–TNF alpha exposed populations as distinct populations. CADTH also accounted for limitations by including relevant comparators, revising the probability of surgery and of post-surgery complications, adjusting costs and resource use, and switching off dose escalation and the loss and regaining of response.

In the anti–TNF alpha naive population, subcutaneous (SC) vedolizumab was dominated by tofacitinib (i.e., tofacitinib was associated with more quality-adjusted life-years [QALYs] at a lower cost compared with vedolizumab SC). In the anti–TNF alpha exposed population, vedolizumab SC was found to be the optimal therapy at a willingness to pay (WTP) above $1,152,959 per QALY gained when compared with tofacitinib. Between a WTP threshold of $117,761 to $1,152,959 per QALY gained, tofacitinib would be the optimal therapy, while below a WTP threshold $117,761 per QALY gained, conventional therapy would be the optimal therapy.

The results of CADTH's reanalysis are highly dependent upon the sponsor's NMA which was characterized by high uncertainty due to limitations and lack of transparency which, in turn, decreases the confidence in the economic results. The purported relative clinical benefits for vedolizumab SC are uncertain. CADTH clinical review concluded [redacted]. The limitations with regard to the sponsor's NMA mean that caution is advised in the interpretation of the pharmacoeconomic results, given the uncertain comparative efficacy between treatments.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

One patient group, the Gastrointestinal (GI) Society, responded to CADTH's call for patient input for the review of vedolizumab SC for the treatment of ulcerative colitis (UC).

Patients noted that UC is a life-long GI condition and that the most frequent symptoms are diarrhea, abdominal pain and cramping, and rectal bleeding. UC can result in extra-intestinal manifestations including fever, inflammation of the eyes or joints (arthritis), ulcers of the mouth or skin, and tender and inflamed nodules on shins. The sponsor included an "active UC" health state within the submitted pharmacoeconomic model that was associated with reduced quality of life and increased resource costs, which may have accounted for some of these complications associated with active UC symptoms.

In addition to the physical symptoms, patients described experiences of anxiety and stress as major factors, with UC having a profound effect on patients' emotional and social life. The sponsor's pharmacoeconomic model modelled patient's quality of life using the EuroQol 5-Dimensions (EQ-5D) instrument. The EQ-5D assesses one's quality of life with regard to five domains: mobility, self-care, usual activities (such as work, study, housework, family and leisure activities), pain/discomfort, and anxiety/depression.[1]

Treatment of UC involves managing the symptoms and consequences of the disease as well as trying to reduce the underlying inflammation. From the patient's perspective, achieving or maintaining remission or treatment response is more important than relieving any one symptom. The sponsor's submitted pharmacoeconomic evaluation modelled treatment efficacy in terms of response and remission as per the Mayo score for UC activity (i.e., which accounts for stool frequency, rectal bleeding, endoscopic findings, and a Physician's Global Assessment).

Economic Review

The current review is for vedolizumab (Entyvio) SC injection (herein referred to as vedolizumab SC) compared with other biologic therapies (vedolizumab IV, adalimumab, infliximab biosimilar, golimumab) or with continuing conventional therapy for the treatment of adult patients with moderately to severely active UC.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis comparing vedolizumab SC with other biologic drugs (adalimumab, infliximab biosimilar, golimumab, vedolizumab IV) or continuing conventional therapy (mesalazine, azathioprine, and prednisolone) in patients with moderately to severely active UC (Mayo score ≥ 6) who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist, in line with its product monograph.[2] The submitted base-case analysis was a mixed population that included both anti–TNF alpha naive and anti–TNF alpha exposed populations (proportions unspecified). Anti–TNF alpha naive and anti–TNF alpha exposed populations were further considered separately in scenario analyses.[2]

The recommended dose of vedolizumab SC as a maintenance treatment, following at least two 300 mg vedolizumab IV infusions, is 108 mg administered by SC injection once every two weeks.[3] The vedolizumab SC regimen captured in the economic model reflected the Health Canada dosing regimen. At the sponsor's reported price of $3,290 for a 300 mg vial of vedolizumab IV, the cost of the initial two IV infusions within the sponsor's model was $6,580. Thereafter, at the sponsor's submitted price of $822.50 per pre-filled syringe or pen for SC injection, the annual cost of vedolizumab SC was $22,208.[2] The dosing of comparators was sourced from product monographs and the costs from the Ontario Drug Benefit Formulary.[4] To reflect real-world practice, dose escalation was modelled using rates of dose escalation informed by real-world sources. The clinical outcomes of interest in the pharmacoeconomic analysis were QALYs.

The pharmacoeconomic analysis was conducted from the perspective of a Canadian publicly funded health care payer over a lifetime time horizon (until patients had reached 110 years of age). Costs and health benefits were both discounted at an annual rate of 1.5%.

Model Structure

All patients entered the model with active UC and received treatment with a biologic drug or conventional therapy. The model structure included a decision tree to capture patient response in the induction phase (10 weeks) and a Markov cohort model to capture long-term outcomes, including those of the maintenance phase.[2] The maintenance phase was modelled using one-year cycles, with half-cycle correction applied.[2]

At the end of 10 weeks, following an induction phase with a biologic treatment or continuation on conventional therapy, patients could achieve response (defined as a reduction of 3 or more points in the complete Mayo score and a ≥ 30% reduction in the complete score from baseline with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point) or remission

(defined as a complete Mayo score of ≤ 2 points and ≤ 1 point in all subscores). Those who do not respond could switch to either conventional therapy, whereby they re-enter the induction phase of the decision tree, or undergo surgery (total colectomy/proctectomy, ileal pouch–anal anastomosis).[2]

Patients who responded in the induction phase entered the Markov model in the corresponding health state (i.e., remission or response). In the Markov cohort model, patients could not transition between the remission and response health states in subsequent cycles. Rather, patients could only sustain remission or response, or lose remission or response and, thereby, transition to the active UC health state.[2] Patients in the active UC state could either remain in that state or transition to the "surgery" health state whereby surgical management was modelled. Immediately following surgery, patients could be in one of two post-surgery states ("post-surgery remission" or "post-surgery complications"). Patients in the post-surgery remission health state could transition to the post-surgery complications health state at any cycle.[2]

Patients on biologic treatment could discontinue treatment due to adverse events or other reasons and switch to conventional therapy, whereby they re-enter the decision tree to reflect the induction phase. Furthermore, while on treatment, patients could experience treatment-related adverse events.[2] Patients could further transition from any health state into an absorbing death health state reflecting all-cause mortality.[2]

Model Inputs

The patient cohort had a mean age of 39.3 years, of which 60.2% were male, as per the VISIBLE 1 clinical trial.[5] A mean weight of 76.0 kg was assumed.[2]

In the absence of head-to-head trial data comparing vedolizumab SC with every biologic comparator in the pharmacoeconomic analysis, the sponsor conducted an NMA [redacted]. The probability of surgery for patients with active UC was derived from the University of Manitoba Inflammatory Bowel Disease Epidemiology Database, as reported by Targownik et al.,[6] and the probability of post-surgery complications (either immediately following surgery or while in the post-surgery remission health state) was derived from Fazio et al.,[7] a study reporting 11 years of outcomes from treating patients with restorative proctocolectomy and ileal pouch–anal anastomoses in the US.

Patients accrued health state–specific QALYs and treatment-related and health state–specific costs as they experienced changes in disease activity, as per their transitions through the different health states within the model. Utility values were sourced from Woehl et al.[8] and Archer et al.[9] The utility value for surgery was calculated based on the assumption that patients would be in the active UC state for eight of the 52 weeks and in the post-surgery remission state for the remaining 44 weeks. Utility decrements associated with adverse events were obtained from the National Institute for Health and Care Excellence (NICE) submission for vedolizumab IV, and it was assumed that all adverse events would have a duration of 10 weeks.[10]

The model included costs for drug acquisition and administration, disease management (by health state), and adverse events. Drug costs were obtained from the Ontario Drug Benefit Formulary using the biosimilar price for infliximab.[4] Resource utilization by health state was informed by two Canadian clinical experts. Unit costs associated with disease management and adverse events were obtained from a variety of sources, including the Ontario Ministry

of Health Schedule of Benefits for Physician Services and Schedule of Benefits for Laboratory Services, and the Ontario Case Costing Initiative.[11-13]

Summary of Sponsor's Economic Evaluation Results

The sponsor's probabilistic cost-effectiveness analysis was based on 10,000 iterations; however, the results were not stable at this number of iterations, with significant run-to-run variation in the ICERs. Given the lack of reliable results from the sponsor's model, CADTH has reported on the deterministic results instead.

Base-Case Results

The sponsor's base-case results (for a mixed population of anti–TNF alpha naive and anti–TNF alpha exposed patients) are presented in Table 3. Only vedolizumab SC and conventional therapy were found to lie on the cost-effectiveness efficiency frontier. Adalimumab, golimumab, infliximab biosimilar, and vedolizumab IV were all dominated in that they were more costly and less effective in terms of QALYs compared with the comparators on the cost-effectiveness efficiency frontier.[2]

Compared with conventional therapy (the least expensive treatment on the cost-effectiveness efficiency frontier), vedolizumab SC was associated with 0.35 incremental QALYs and an incremental cost of $35,304. The ICER for vedolizumab SC was $100,582 per QALY gained compared with conventional therapy.[2] At a WTP threshold of $50,000 per QALY, vedolizumab SC would not be considered cost-effective.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)[a]
Conventional therapy	840,191	14.0232	–
Vedolizumab SC	875,495	14.3742	$100,582

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous.

Note: Given the instability in the sponsor's probabilistic analysis, CADTH has reported the sponsor's deterministic results. Only treatments that are on the efficiency frontier are reported. Detailed results, including treatments that are not on the cost-effectiveness efficiency frontier, can be found in Appendix 3.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table, as QALYs were rounded up to only four decimal places.

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

Sensitivity and Scenario Analysis Results

The sponsor-conducted sensitivity and scenario analyses. These included assessing the anti–TNF alpha naive and the anti–TNF alpha exposed populations as separate subgroups; varying the rate of dose escalation (0% to 100%); including ustekinumab and tofacitinib as comparators; assuming treatment waning; taking a societal perspective; and exploring different discount rates (0% and 3.5%). In the anti–TNF alpha naive subgroup, the deterministic ICER for vedolizumab SC increased to $105,042 per QALY compared with conventional therapy. Vedolizumab IV was also on the cost-effectiveness efficiency frontier, with a deterministic ICER of $163,515 per QALY compared with vedolizumab SC. In the anti–TNF alpha exposed subgroup, the deterministic ICER for vedolizumab SC increased to $108,090 per QALY compared with conventional therapy. Further details of the deterministic results of the sponsor's sensitivity and scenario analyses are presented in Table 12.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations of the sponsor's analysis that have notable implications on the economic analysis:

- **Comparative treatment efficacy is uncertain:** Relative treatment efficacy was based on the sponsor-conducted NMA that had limited applicability. The CADTH clinical review noted that no information was provided with regard to the study identification process or to the inclusion and exclusion criteria. Studies selected for inclusion in the sponsor's NMA were based on a previously conducted systematic review with no citation given on the systematic search or the study-selection process, and not all eligibility criteria were defined a priori. This lack of transparency introduced the potential for bias in the results. A recent systematic review with a similar research question found 17 different clinical trials; of those, three were not included in the sponsor's NMA. [redacted]. Imprecision in the effect estimates (wide credible intervals) were noted due to small sample sizes. Furthermore, there was no analysis conducted to account for trial and clinical heterogeneity in any manner that would be useful. The major concern with the trial heterogeneity is how trials managed patients in the transition from the induction to the maintenance phase. For example, in five of the trials, responders in the induction phase were re-randomized upon entering the maintenance phase, while the other trials allowed the patients to continue through. Additionally, there were differences in outcome definition between the trials, which may also make it more challenging to compare across trials indirectly in meaningful ways. Significant differences were noted in baseline characteristics, including factors that may be associated with disease severity such as age, C-reactive protein, prior treatment failure, and years of active disease. Collectively, these limitations limit the utility and the robustness of the results from the NMA, which were subsequently used to inform the relative treatment efficacy parameters within the economic model.
    - Despite the concerns with the validity of the sponsor's NMA and, hence, the relative efficacy inputs incorporated into the economic model, CADTH was unable to a conduct reanalysis to assess this limitation. The cost-effectiveness findings of the pharmacoeconomic model must therefore be interpreted with caution.
- **Sponsor's results were unstable:** The probabilistic ICERs reported in the pharmacoeconomic models for the anti–TNF alpha naive and anti–TNF alpha exposed populations were unstable at 10,000 iterations. CADTH conducted multiple probabilistic model runs at 10,000 iterations and found that the resulting ICERs were substantially different between runs. The model further did not allow the number of Monte Carlo simulations to exceed 10,000 iterations. CADTH investigated the causes underlying the instability in the submitted economic model and noted two likely reasons: the wide credible intervals associated with relative risk estimates, and the arbitrary definition of uncertainty for many of the model parameters. The CADTH clinical review noted imprecision in the comparative treatment effect estimates, as demonstrated by the considerably wide credible intervals around many of the treatment effect estimates in the sponsor's NMA. This uncertainty in the relative treatment effects was therefore introduced into the economic model. In addition, for many of the model parameters, the standard error of the mean was set to 10% of the mean. No appropriate justifications were provided for this assumption. The approach to define uncertainty for all parameters (other than the relative effect estimates in the induction and maintenance phase and the discontinuation rates due to adverse events in the maintenance phase) was inappropriate, as the

resultant ICERs do not reflect the true uncertainty within the model's input values. The instability in the ICERs means that one cannot draw reliable conclusions with regard to the probabilistic cost-effectiveness results.

- Although CADTH guidelines require analyses to be probabilistic, CADTH conducted deterministic analyses as part of its reanalysis, given the lack of reliability in the probabilistic analyses.

- **Exclusion of relevant comparators from the base case:** The sponsor excluded tofacitinib and ustekinumab from its submitted base case on the grounds that it is not funded by provincial drug formularies. Both comparators do, however, have notices of compliance from Health Canada, and ustekinumab is currently being reviewed by CADTH while tofacitinib received a positive recommendation by the CADTH Canadian Drug Expert Committee (CDEC) in 2019.[15]
  - Given that ustekinumab is currently being reviewed by CADTH and that tofacitinib was recommended by CDEC in 2019, CADTH included these two comparators. Minor errors in the unit costs and dosages of these comparators were noted within the model and corrected by CADTH.
- **Overestimation in surgery-related parameters:** The rate of patients undergoing UC-related surgery in Canada was derived from the University of Manitoba Inflammatory Bowel Disease Epidemiology Database, as reported by Targownik et al.[6] The sponsor took the 10-year risk of surgery (10.4%) and converted it to a 10-week probability to estimate the number of nonresponders undergoing surgery during the induction phase, and to an annual probability to estimate the number of patients in the active UC health state undergoing surgery in the maintenance phase (i.e., 0.09% and 0.46%, respectively). The Targownik et al. study does, however, report the 20-year risk of surgery (14.80%).[6] According to the clinical expert consulted by CADTH, the use of longer-term data would have been more appropriate, given the lifetime time horizon of the model.[6] This would have translated to a 10-week probability and an annual probability of 0.07% and 0.34%, respectively.

  Additionally, the sponsor applied a 50.7% annual probability of experiencing post-surgery complications, which was sourced from a study conducted in the US by Fazio et al. (1995).[7] According to the clinical expert consulted by CADTH, an annual probability of 50.7% is exceptionally high, as they would expect only a small minority of patients to have complications each year. Upon inspection of the Fazio et al. (1995) study, CADTH reviewers noted that the probability of late complications (complications such as pouchitis, small bowel obstruction, and anal stricture 30 days after surgery) was reported to be 50.5% over a median follow-up period of 32.06 months.[7] Assuming that the rates are linear, if this was converted to an annual probability, this would be equal to 23.1%. Furthermore, the study demonstrated a lower rate of complications between 1989 and 1993 (44.2%) compared with 1983 and 1988 (63.7%), which is indicative of a downward trend in the incidence rate of post-surgical complications over time. Suzuki et al. conducted a more recent study with a longer duration.[16] In this study, they reported the cumulative risk of pouchitis at one year (10.7%), two years (17.2%), five years (24.0%), and 10 years (38.2%). Although this study was conducted in Japan, the clinical expert consulted by CADTH considered these probabilities to be more generalizable and reflective of current Canadian clinical practice.

  - CADTH converted the 20-year risk of surgery to derive both 10-week and annual probabilities of surgery in the induction and maintenance phases, respectively. CADTH further converted the 10-year probability of post-surgical complication (38.2%) from

Suzuki et al.[16] into an annual probability (4.7%) of patients moving to the post-surgery complications health state.

- **Surgery-related costs were calculated inappropriately:** For the variable-costs parameters, the sponsor took a micro-costing approach in which resource use (in terms of the number of units per type of resource) were estimated for an eight-week period. These were subsequently converted to either 10 weeks to reflect the expected resource use over the entire duration of the decision tree (induction phase), or to one year to reflect the one-year cycle within the Markov model (maintenance phase). The costs associated with surgery and post-surgery complications were estimated based on the Ontario Case Costing Initiative, which reports the total cost by case (i.e., fixed costs).[13] As such, according to the sponsor's submitted pharmacoeconomic report, these costs should be considered one-time costs. Yet, within the economic model, these costs were incorrectly adjusted, as per the method described earlier. In effect, this overestimates the costs of surgery and post-surgery complications.

  Furthermore, within the surgery health state, the sponsor included both a cost for the surgical procedure and a cost for hospitalization. The cost of the surgical procedure was informed by the Ontario Case Costing Initiative (OCCI) costing tool which reflects the inpatient cost for the surgical procedure from admission to discharge.[11,13] As the OCCI's cost includes the cost of hospitalization, the sponsor's approach to add a cost for hospitalization in effect double counts the cost of hospitalization associated with the surgical procedure.

  - CADTH revised the cost of surgery and post-surgery complications as one-time costs and removed the cost of hospitalization within the surgery health state.

- **Resource use not reflective of clinical practice:** According to the clinical expert consulted by CADTH, the resource use over an eight-week period for each health state, as shown in Table 13, was not reflective of clinical practice in Canada. Some notable feedback provided by the clinical expert was that: inflammatory bowel disease nurses and psychologists are rarely available in the treatment of UC; that one would not expect more than two colonoscopies to be performed per year on patients in the active UC health state; that two to four visits to a gastroenterologist would be expected for the treatment of post-surgery complications; and that performing a colonoscopy in the remission health states would be rare (i.e., one colonoscopy every four to five years in the post-surgery remission). CADTH amended the resource use to reflect the advice of the clinical expert (Table 18).

- **Inconsistencies in the application of dose escalation and loss and regaining of response:** The sponsor assumed dose escalation for golimumab and the infliximab biosimilar (and also for ustekinumab and tofacitinib in the sponsor's scenario analyses). No dose escalation was applied for adalimumab, vedolizumab SC, or vedolizumab IV. Although the proportions were claimed to be informed by real-world sources, these proportions are unlikely to align with the NMA inputs that informed the relative efficacy of treatments. According to the clinical expert consulted by CADTH, a dose-response relationship exists, as patients who receive an escalated dose are expected to more likely achieve clinical response/remission compared with those receiving the Health Canada–approved dosing schedule. It is therefore important that the proportion of patients receiving an escalated dose within the economic model be consistent with the proportions that were studied within the included clinical trials that informed the model's comparative efficacy data. However, given the limited reporting noted earlier regarding

the sponsor's submitted NMA, the proportions of patients receiving an escalated dose within the included trials could not be confirmed by CADTH.

Furthermore, outside of tofacitinib, the assumptions on dose escalation did not align with the drug's product monograph. According to the product monograph for golimumab, a maintenance dose of 100 mg every four weeks may be considered, as opposed to the regular maintenance dose of 50 mg every four weeks. Yet, in the sponsor's pharmacoeconomic model, patients receiving the higher dose were assumed to receive 100 mg every two weeks. The same limitation applies to how dose escalation was applied to the infliximab biosimilar, whereby patients receiving an escalated dose received both more a frequent and higher dose: 10 mg/kg every four weeks, as opposed to 5 mg/kg every eight weeks. The product monograph for infliximab states only that the dose may be increased to 10 mg/kg without a reference to an increased dose frequency. The sponsor assumed an escalated dose of ustekinumab from 90 mg every eight weeks to 90 mg every four weeks, despite the product monograph making no reference to dose escalation.

The sponsor also assumed that patients receiving golimumab, infliximab, tofacitinib, and ustekinumab would lose response, but that some of these patients might regain response. It is uncertain why this was applied to only a select few biologics. and whether this aligned with the clinical studies informing the submitted NMA, given a lack of sufficient reporting. CADTH turned off the options for dose escalation and loss and regaining of response.

- **Combining subgroups into a mixed population for the base case rather than conducting stratified analyses:** The sponsor's primary treatment population consisted of a mixed anti–TNF alpha naive or anti–TNF alpha exposed population, which is consistent with the approved indication and reimbursement request. However, according to the sponsor's submitted NMA[2] and feedback from the clinical expert consulted by CADTH, the relative efficacy between treatment differs between the anti–TNF alpha naive and the anti–TNF alpha exposed populations. As such, it would have been more appropriate to conduct stratified analyses, modelling separate populations in the base case, as per CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada*.[17]
    - CADTH assessed these two distinct populations separately in its reanalysis (one analysis for anti–TNF alpha naive patients and another for anti–TNF alpha exposed patients). Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comments
After discontinuation of a biologic, patients switch to conventional therapy.	According to the clinical expert consulted by CADTH, patients would typically switch to another biologic. However, given the uncertainty surrounding treatment sequences, this was an acceptable simplifying assumption.
Patients starting conventional therapy cannot switch at any point to a biologic.	According to the clinical expert consulted by CADTH, patients who discontinue conventional therapy would likely switch to a biologic therapy, although this was acceptable as a simplifying assumption.
Patients who receive conventional therapy do not discontinue treatment due to treatment-related AEs or other reasons.	This is uncertain, although acceptable as a simplifying assumption.

Sponsor's key assumption	CADTH comments
Patients receiving biologic therapy will discontinue treatment upon transitioning to the active UC health state from either the remission or response health states.	Acceptable.
The cost of the surgical procedure is assumed to include the cost of managing early surgical complications occurring within a month of the surgical procedure.	Acceptable.
Patients are assumed to receive the surgery only once in their lifetime.	Acceptable as a simplifying assumption.
Patients are assumed to not be at any additional risk of mortality due to UC, treatment-related AEs, surgery, or surgery-related complications.	Uncertain, but unlikely to impact the model.

AE = adverse event; TNF = tumour necrosis inhibitor; UC = ulcerative colitis.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH undertook reanalyses that addressed limitations within the model, as summarized in Table 5. Additionally, CADTH made corrections to the sponsor's model. Given the instability in the probabilistic ICERs CADTH conducted all reanalyses and price-reduction analyses deterministically.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Corrected the unit cost of adalimumab	$962.46 per 40 mg/0.8 mL syringe	$769.97 per 40 mg/0.8 mL syringe[4]
2. Corrected the dose of golimumab	200 mg at week 0, 100 mg at week 2, and 100 mg at week 4 followed by 100 mg every 4 weeks	200 mg at week 0, 100 mg at week 2, 50 mg at week 6, 0 mg at week 8, and 50 mg every 4 weeks[18]
3. Included the cost of a dietician and a psychologist (for cost of post-surgery remission health state)	Cost of a dietician and psychologist was excluded	Cost of a dietician and psychologist was included
Changes to derive the CADTH base case		
1. Combining subgroups into a mixed population for the base case	Mixed (anti–TNF alpha naive and anti–TNF alpha exposed) population	Stratified analysis assessing the anti–TNF alpha naive and the anti–TNF alpha exposed populations separately
2. Exclusion of relevant comparators from the base case	Excluded ustekinumab and tofacitinib	Included ustekinumab and tofacitinib
3. Overestimation in surgery-related parameters: Probability of surgery	10-year risk of surgery (10.4%) from Targownik et al. (2012) was converted to 10-week and annual probabilities[6]	20-year risk of surgery (14.80%) from Targownik et al. (2012) was converted to 10-week and annual probabilities[6]
4. Overestimation in surgery-related parameters: Probability of post-surgery complications	Applied a 50.7% annual probability of post-surgery complications (from Fazio et al. [1995]) in the surgery and post-surgery remission health state[7]	Converted a 10-year probability of pouchitis (38.2%) from Suzuki et al. (2012) into an annual probability[16]
5. Surgery-related costs were calculated inappropriately	10-week costs for surgery and post-surgery complications were treated as	Cost of surgery and post-surgery complications treated as one-time costs

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
	recurrent costs (i.e., multiplied by 5.22, the number of 10-week cycles in a year)	
6. Resource use not reflective of clinical practice	Resource use not reflective of clinical practice in Canada; cost of hospitalization in the surgery health state was double counted	Resource use amended to reflect Canadian clinical practice and the cost of hospitalization was removed from the surgery health state as it is already accounted for in the cost of a surgical procedure
7. Inconsistencies in the application of dose escalation and loss and regaining of treatment response	Dose escalation and loss and regaining of treatment response applied in the model	Dose escalation and loss and regaining of response removed from the model
CADTH base case		Corrected sponsor base case plus reanalyses 1, 2, 3, 4, 5, 6, and 7

TNF = tumour necrosis factor.

CADTH undertook a stepped analysis, incorporating each change proposed in Table 5 into the sponsor's corrected base case to highlight the impact of each change, as presented in Table 14 and Table 15 for the anti–TNF alpha naive and the anti–TNF alpha exposed populations, respectively. The summary results of the sponsor's corrected base case and the CADTH reanalysis are presented in Table 6 and Table 7 for the anti–TNF alpha naive and the anti–TNF alpha exposed populations, respectively.

In the anti–TNF alpha naive population of the CADTH reanalysis, only conventional therapy and tofacitinib were on the cost-effectiveness efficiency frontier. The ICER for tofacitinib compared with conventional therapy was $91,883 per QALY gained. Vedolizumab SC was dominated by tofacitinib in that vedolizumab SC was associated with additional costs and fewer QALYs. All other comparators were dominated or extendedly dominated.

In the anti–TNF alpha exposed population, conventional therapy, vedolizumab SC, and tofacitinib were on the cost-effectiveness efficiency frontier. Vedolizumab SC had an ICER of $1,152,959 per QALY gained compared with tofacitinib. Tofacitinib had an ICER of $117,761 per QALY gained compared with conventional therapy. All other comparators were dominated or extendedly dominated.

Table 6: Summary of the CADTH Reanalysis Results in the Anti–TNF Alpha Naive Subgroup

Drug	Total costs ($)	Total QALYs	ICER versus conventional therapy	Sequential ICER ($)[a]
Sponsor-corrected base case				
Conventional therapy	837,414	14.0675	–	–
Vedolizumab SC	874,110	14.4170	$105,021	105,021
Vedolizumab IV	876,210	14.4298	$107,094	163,482
CADTH base case				
Conventional therapy	374,548	13.9139	–	–
Tofacitinib	414,415	14.3478	$91,883	91,883
Vedolizumab SC	427,126	14.2740	$146,005	Dominated by tofacitinib

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous.

Note: Given the instability in the sponsor's probabilistic analysis, CADTH has reported the sponsor's deterministic results. Only treatments that are on the efficiency frontier are reported with the exception of vedolizumab SC. Detailed results, including treatments that are not on the cost-effectiveness efficiency frontier, can be found in Appendix 4.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table, as QALYs were rounded up to only four decimal places.

Table 7: Summary of the CADTH Reanalysis Results in the Anti–TNF Alpha Exposed Subgroup

Drug	Total costs ($)	Total QALYs	ICER versus conventional therapy	Sequential ICER ($)[a]
Sponsor-corrected base case				
Conventional therapy	853,264	13.8402	–	–
Vedolizumab SC	882,783	14.1133	$108,061	108,061
CADTH base case				
Conventional therapy	380,078	13.6809	–	–
Tofacitinib	412,396	13.9553	$117,761	117,761
Vedolizumab SC	424,256	13.9656	$155,159	1,152,959

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous.

Note: Given the instability in the sponsor's probabilistic analysis, CADTH has reported the sponsor's deterministic results. Only treatments that are on the efficiency frontier are reported. Detailed results, including treatments that are not on the cost-effectiveness efficiency frontier, can be found in Appendix 4.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table, as QALYs were rounded up to only four decimal places.

Detailed results of CADTH base case for the anti–TNF alpha naive and anti–TNF alpha exposed population are presented in Table 16 and Table 17, respectively. CADTH identified that the key driver of the model results were the relative efficacy parameters. Specifically, patients receiving vedolizumab SC spent more time in the maintenance phase in the response and remission health states compared with other comparators resulting in substantially lower disease management costs.

Scenario Analysis Results

CADTH conducted a scenario analysis in both the anti–TNF alpha naive (Table 19) and the anti–TNF alpha exposed (Table 20) populations whereby loss and regaining of response

were applied for golimumab, the infliximab biosimilar, tofacitinib, and ustekinumab. In the anti–TNF alpha naive population; conventional therapy, the infliximab biosimilar, and vedolizumab IV were on the cost-effectiveness efficiency frontier. Vedolizumab SC was extendedly dominated by the infliximab biosimilar and vedolizumab IV. In the anti–TNF alpha exposed population; conventional therapy, vedolizumab SC, and tofacitinib were on the cost-effectiveness efficiency frontier. Vedolizumab SC had an ICER of $297,961 per QALY gained compared with tofacitinib.

CADTH also conducted price-reduction analyses (Table 8) on the sponsor's corrected base case (mixed population) and on the CADTH base case (separately for the anti–TNF alpha naive and the anti–TNF alpha exposed populations). In the CADTH reanalysis, price reductions of at least 61% and 65% are required for vedolizumab SC to be considered cost-effective at a WTP of $50,000 per QALY in the anti–TNF alpha naive and the anti–TNF alpha exposed populations, respectively.

Table 8: CADTH Price-Reduction Analyses

	ICERs for vedolizumab SC versus comparators		
Price reduction	**Sponsor-corrected base case (mixed population)**	**CADTH reanalysis (anti–TNF alpha naive)**	**CADTH reanalysis (anti–TNF alpha exposed)**
No price reduction	$100,560 (versus CT)	Vedolizumab SC is dominated	$1,152,959 (versus tofacitinib)
10%	$84,938 (versus CT)	Vedolizumab SC is dominated	$710,560 (versus tofacitinib)
20%	$69,316 (versus CT)	Vedolizumab SC is dominated	$268,162 (versus tofacitinib)
30%	**$53,694 (versus CT)**	Vedolizumab SC is extendedly dominated	$107,212 (versus CT)
40%	$38,071 (versus CT)	$84,012 (versus CT)	$91,230 (versus CT)
50%	$22,449 (versus CT)	$68,514 (versus CT)	$75,247 (versus CT)
60%	$6,827 (versus CT)	$53,016 (versus CT)	$59,265 (versus CT)
61%	$5,265 (versus CT)	$51,466 (versus CT)	$57,667 (versus CT)
62%	$3,702 (versus CT)	**$49,916 (versus CT)**	$56,069 (versus CT)
65%	Vedolizumab SC is dominant	$45,267 (versus CT)	$51,274 (versus CT)
66%	Vedolizumab SC is dominant	$43,717 (versus CT)	**$49,676 (versus CT)**
70%	Vedolizumab SC is dominant	$37,518 (versus CT)	$43,283 (versus CT)

CT = conventional therapy; ICER = incremental cost-effectiveness ratio; SC = subcutaneous.

Issues for Consideration

- According to the clinical expert consulted by CADTH, vedolizumab should be prescribed in an outpatient specialty clinic, such as one specializing in gastroenterology or internal medicine. Following appropriate training, vedolizumab SC would likely be administered by the patient at home.
- The CADTH Common Drug Review (CDR) previously reviewed vedolizumab IV in October 2015 for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist. The CDEC recommendation came with a pricing condition that there be "a reduction in price to improve the cost-effectiveness of vedolizumab to a level acceptable to the drug plans."[19] Additionally, CDR previously reviewed vedolizumab IV in October 2016 for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha

antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids. The CDEC recommendation came with a pricing condition that "the cost of treatment with vedolizumab should not exceed the drug plan cost of the least costly alternative biologic treatment option."[20]

Overall Conclusions

In the sponsor's pharmacoeconomic model, vedolizumab SC and conventional therapy were the only comparators to lie on the cost-effectiveness efficiency frontier. Vedolizumab SC had a deterministic ICER of $100,582 per QALY gained compared with conventional therapy. However, this result warranted careful interpretation due to uncertain comparative treatment efficacy; unstable probabilistic analyses; the exclusion of relevant comparators; overestimated values for the probability of surgery and post-surgery complications; inappropriate costing and resource use that does not reflect clinical practice; and uncertainty in the application of dose escalation and loss and regaining of response.

CADTH attempted to address most of these issues in the CADTH reanalysis and further separated the anti–TNF alpha naive and anti–TNF alpha exposed populations as stratified analyses. In the anti–TNF alpha naive population, vedolizumab SC was dominated by tofacitinib (tofacitinib was associated with more QALYs at a lower cost compared with vedolizumab SC). In the anti–TNF alpha exposed population, vedolizumab SC had an ICER of $1,152,959 per QALY gained compared with tofacitinib. Between a WTP threshold of $117,761 to $1,152,959 per QALY gained, tofacitinib would be the optimal therapy, while below a WTP threshold $117,761 per QALY gained, conventional therapy would be the optimal therapy. Price reductions of at least 61% and 65% are required for vedolizumab SC to be considered cost-effective at a WTP threshold of $50,000 per QALY in the anti–TNF alpha naive and the anti–TNF alpha exposed populations, respectively.

Caution is advised in the interpretation of the CADTH reanalysis. The results of CADTH's reanalysis are highly dependent upon the sponsor's NMA, which was characterized by high uncertainty due to limitations and lack of transparency which, in turn, decreases the confidence in the results. The purported relative clinical benefits for vedolizumab SC are uncertain. The CADTH clinical review concluded that [redacted]. The limitations with regard to the sponsor's NMA mean that caution is advised in the interpretation of the pharmacoeconomic results, given the uncertain comparative efficacy between treatments.

It should be further noted that the annual cost of vedolizumab SC would be $25,501 and $21,385 per patient in the first and subsequent years, respectively. Based on publicly available prices, the annual cost of an infliximab biosimilar, the least costly biologic for this indication, is $15,776 and $13,804 in the first and subsequent years, respectively.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 9: CADTH Cost Comparison Table for Ulcerative Colitis

Drug and comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average cost per month ($)	Average cost per year ($)
Vedolizumab (Entyvio) (SC)	**300 mg** **108 mg/0.68 mL**	**Vial for IV infusion** **Pre-filled syringe or pen for SC injection**	**3,291.0000[a]** **822.5000**	**300 mg for at least two IV infusions followed by 108 mg SC every 2 weeks thereafter**	**Year 1: 2,125.04 Thereafter: 1,782.08**	**Year 1: 25,501[b] Thereafter: 21,385**
Comparators: Biologics						
Adalimumab (Humira)	40 mg/0.8 mL	Pre-filled syringe or auto-injector for SC injection	769.9700	160 mg at week 0, 80 mg at week 2, then 40 mg every other week thereafter[c]	Year 1: 1,924.93 Thereafter: 1,668.27	Year 1: 23,099 Thereafter: 20,019
Golimumab (Simponi)	50 mg/0.5 mL 100 mg/1 mL	Pre-filled syringe or auto-injector for SC injection	1,555.1700[a] 1,557.0000[a]	200 mg at week 0, 100 mg at week 2, then 50 mg every 4 weeks thereafter[d]	Year 1: 1,944.42 Thereafter: 1,684.77	Year 1: 23,333 Thereafter: 20,217
Infliximab biosimilar (Inflectra)	100 mg	Vial for IV infusion	525.0000	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter[e]	Year 1: 1,400.00 Thereafter: 1,225.00	Year 1: 16,800 Thereafter: 14,700
Infliximab biosimilar (Remicade)	100 mg	Vial for IV infusion	977.0000[ba]	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter[f]	Year 1: 2,605.33 Thereafter: 2,279.67	Year 1: 31,264 Thereafter: 27,356
Infliximab biosimilar (Renflexis)	100 mg	Vial for IV infusion	493.0000	5 mg/kg at week 0, 2, and 6, then every 8 weeks thereafter[g]	Year 1: 1,314.67 Thereafter: 1,150.33	Year 1: 15,776 Thereafter: 13,804

Drug and comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average cost per month ($)	Average cost per year ($)
Tofacitinib (Xeljanz)	5 mg 10 mg	Tablet	23.9589 42.3436[h]	10 mg twice daily for at least 8 weeks, then 5 mg twice daily thereafter	Year 1: 1,625.10 Thereafter: 1,453.51	Year 1: 19,501 Thereafter: 17,442
Ustekinumab (Stelara)	130 mg/26.0 mL 90 mg/1.0 mL	Vial for IV infusion Pre-filled syringe for SC injection	2,080.0000[a] 4,593.1400	6 mg/kg IV at week 0, then 90 mg SC every 8 weeks thereafter[i]	Year 1: 2,816.57 Thereafter: 2,679.33	Year 1: 33,799 Thereafter: 32,152
Vedolizumab (Entyvio) (IV only)	300 mg	Vial for IV infusion	3,291.0000[a]	300 mg at week 0, 2, and 6, then every 8 weeks thereafter[j]	Year 1: 2,149.00 Thereafter: 1,919.75	Year 1: 26,328 Thereafter: 23,037
Comparators: Aminosalicylates						
5-ASA (Asacol, Asacol 800)	400 mg 800 mg	Tablet	0.5597 1.1358	Active: 2 to 8 tablets daily in divided doses Maintenance: 4 tablets daily in divided doses[k]	34.05 to 136.19	409 to 1,634
5-ASA (Mesasal)	500 mg	Enteric tablet	0.6559	Active: 1.5 g to 3 g tablets daily in divided doses Maintenance: 1.5 g daily in divided doses[l]	59.85 to 119.70	718 to 1,436
5-ASA (Mezavant)	1.2 g	Delayed extended release tablet	1.7284	Active: 2 to 4 tablets once daily Maintenance: 2 tablets daily[m]	105.14 to 210.29	1,262 to 2,523
5-ASA (Pentasa)	500 mg 1,000 mg	Extended release tablet	0.5881 1.1761	0.5 g to 1 g four times daily (2 g daily dose)[n]	71.55 to 143.09	859 to 1,717
	1 g	Suppository	1.9962	1 g daily[n]	60.72	729
	1 g/100 mL 4 g/100 mL	Enema Enema	4.4790 6.0400	1 g to 4 g daily	136.24 to 183.72	1,635 to 2,205
5-ASA (Salofalk)	500 mg	Enteric tablet	0.6445	Active: 3 g to 4 g daily in divided doses[o]	117.62 to 156.83	1,411 to 1,882

Drug and comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average cost per month ($)	Average cost per year ($)
				Maintenance: 1.5 g to 3 g per day in divided doses[o]		
	500 mg 1,000 mg	Suppository Suppository	1.5314 2.2495	1 g to 1.5 g per day[c]	68.42 to 115.00	821 to 1,380
	4 g/60 g	Rectal suppository	8.1360	Active: 4 g nightly Maintenance: 2 g nightly or 4 g every two nights	247.47 123.74	2,970 1,485
Olsalazine (Dipentum)	250 mg	Capsule	0.5330	Active: 1 g to 3 g daily in divided doses[h] Maintenance: 1 g daily in divided doses[h]	Year 1: 64.85 to 194.55 Thereafter: 64.85	Year 1: 778 to 2,335 Thereafter: 778
Sulfasalazine (Salazopyrin, generics)	500 mg	Tablet	0.1804	Active: 1 g to 2 g three to four times daily[o] Maintenance: 1 g two to three times daily[o]	Year 1: 32.92 to 87.89 Thereafter: 21.95 to 32.92	Year 1: 395 to 1,054 Thereafter: 263 to 395
Comparators: Corticosteroids						
Betamethasone enema (Betnesol)	5mg/100mL	Enema	11.8214	5 mg nightly[h]	359.57	4,315
Budesonide (Entocort)	3 mg	Capsule	1.8653[ba]	3 mg three times per day up to 8 weeks, followed by 6 mg daily for up to 3 month[h]	54.48	654
Hydrocortisone enema (Cortenema, Cortifoam)	100 mg/ 60 mL	Enema	8.2541	60 mL nightly or every other night	125.53 to 251.06	1,506 to 3,013
	15 g/pack (14 doses)	Rectal aerosol	117.8800	One dose nightly or every other night[h]	117.88 to 235.80	1,415 to 2,830
Hydrocortisone (Solu-Cortef)	100 mg 250 mg	Vial	4.1500[ba] 7.2000[ba]	100 mg to 500 mg IV daily to induce remission, then switch to other drug[h]	126.25 to 438.00	1,515 to 5,256
Prednisone (generic)	1 mg 5 mg 50 mg	Tablet	0.1095[a] 0.0220 0.1735	40 mg to 60 mg daily to induce remission, then lower dose[h]	5.42 to 8.08	65 to 79 or lower

Drug and comparator	Strength	Dosage form	Price ($)	Recommended dosage	Average cost per month ($)	Average cost per year ($)
Comparators: Immunomodulators						
Azathioprine (generic)	50 mg	Tablet	0.2405	up to 2.5 mg/kg daily[h]	29.26	351
Azathioprine (Imuran)	50 mg	Tablet	1.0927		132.95	1,595
Mercaptopurine (Purinethol and generic)	50 mg	Tablet	2.8610	1.5 mg/kg to 2.5 mg/kg daily[h]	261.07 to 348.09	3,133 to 4,177
Methotrexate (generic)	2.5 mg 10 mg	Tablet	0.6325 2.7000[a]	10 mg to 25 mg weekly[h]	11.70 to 28.88	140 to 347

5-ASA = 5-aminosalicylic acid; SC = subcutaneous.

Note: All weight-based calculations based on an assumed mean weight of 73.2 kg, taken from sponsor's baseline patient characteristics, and assumes wastage.

[a] Price obtained from the Saskatchewan Drug Benefit (August 2019). The price for ustekinumab was reported as $16.0000 per unit which, when adjusting for 130 units, resulted in a price of $2,080.

[b] Only two IV doses are assumed.

[c] Health Canada Drug Product Database.

[d] Product monograph for Simponi (golimumab) injection.

[e] Product monograph for infliximab biosimilar Inflectra.

[f] Product monograph for infliximab biosimilar Remicade.

[g] Product monograph for infliximab biosimilar Renflexis.

[h] Xeljanz CADTH Common Drug Review Pharmacoeconomic Report.

[i] Product monograph for ustekinumab (Stelara).

[j] Product monograph for vedolizumab.

[k] 5-ASA Asacol.

[l] 5-ASA Mesasal.

[m] 5-ASA Mezavant.

[n] 5-ASA Pentasa.

[o] RxTx.

Source: Ontario Drug Benefit Formulary/Comparative Drug Index (effective August 2019) unless otherwise noted; annual period assumes 52 weeks, 365 days.

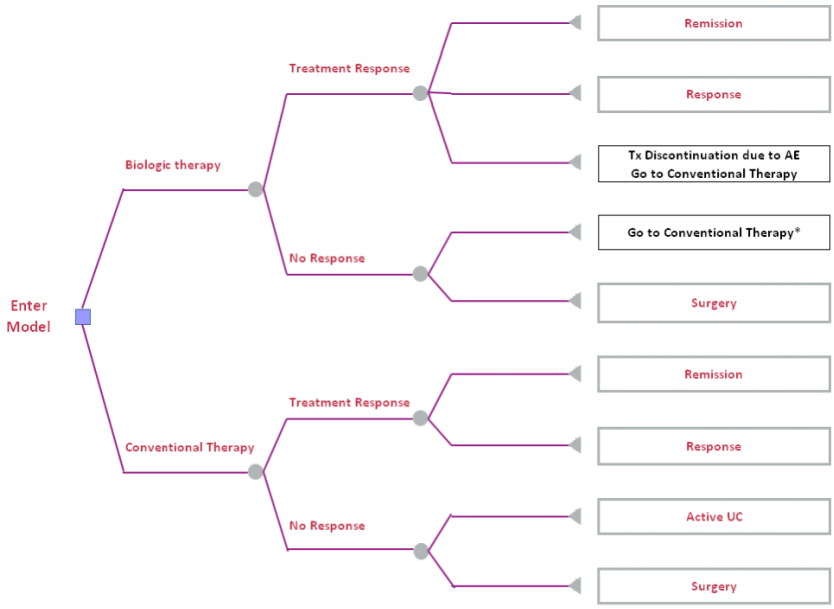
Appendix 2: Submission Quality

Table 10: Submission Quality

	Yes	No	Comments
Population is relevant, with no critical intervention missing and no relevant outcome missing.	☒	☐	Population was relevant. Two relevant comparators were excluded from the base-case analysis; however, the sponsor did allow for these to be easily included.
Model has been adequately programmed and has sufficient face validity.	☐	☒	There were many programming errors within the model, including incorrect conversion of probabilities into the appropriate cycle length.
Model structure is adequate for decision problem.	☒	☐	The model structure was adequate.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	☐	☒	Parameters, such as some drug unit costs, were incorrect.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	☐	☒	Probabilistic results were unstable at 10,000 iterations. This was likely due to the wide credible intervals in the relative treatment effect parameters. The sponsor also used an arbitrary definition of uncertainty for all model parameters other than the relative effect estimates and the discontinuation rates due to adverse events in the maintenance phase. The arbitrary definition used was that the standard error of the mean was estimated to be 10% of the mean.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough detail).	☐	☒	There were many discrepancies between the submitted pharmacoeconomic model and pharmacoeconomic report.

Appendix 3: Detailed Information on the Submitted Economic Evaluation

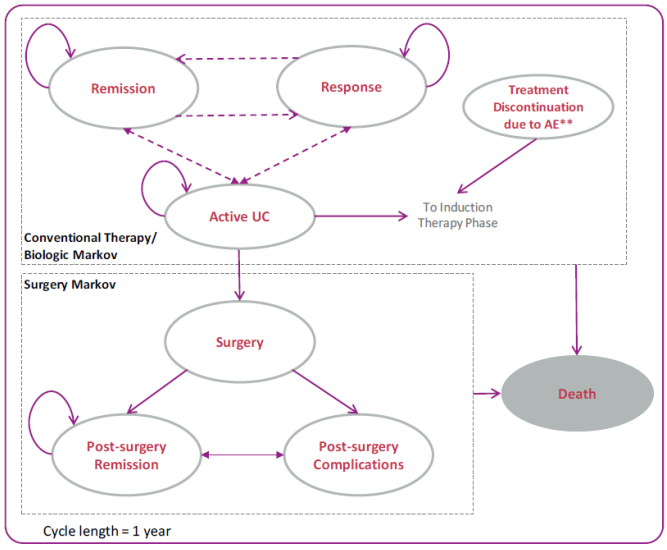
Figure 1: Model Structure – Induction Phase



AE = adverse event.

Source: Sponsor's pharmacoeconomic submission.[21]

Figure 2: Model Structure – Maintenance Phase



AE = adverse event; UC = ulcerative colitis.

** Applies only to patients who had a biologic therapy at the onset.

Source: Sponsor's pharmacoeconomic submission.[21]

Table 11: Detailed Results of the Sponsor's Base Case (Deterministic)

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Conventional therapy	840,191	14.0232	–
Vedolizumab SC	875,495	14.3742	$100,582
Infliximab biosimilar	875,671	14.2375	Dominated by vedolizumab SC
Golimumab	875,793	14.1571	Dominated by vedolizumab SC and infliximab biosimilar
Vedolizumab IV	877,849	14.3316	Dominated by vedolizumab SC
Adalimumab	885,143	14.1372	Dominated by vedolizumab SC, golimumab, infliximab biosimilar and vedolizumab IV

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous.

Table 12: Sponsor's Scenario Analyses (Deterministic)

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($/QALYs)[a]
Sponsor's base case (mixed population)	Conventional therapy	840,191	14.0232	–
	Vedolizumab SC	875,495	14.3742	100,582
Anti–TNF alpha naive subgroup	Conventional therapy	837,313	14.0675	–
	Vedolizumab SC	874,017	14.4170	105,042
	Vedolizumab IV	876,118	14.4298	163,515
100% dose escalation (mixed population)	Conventional therapy	840,191	14.0232	–
	Vedolizumab SC	926,716	14.3742	246,512
No dose escalation (mixed population)	Conventional therapy	840,191	14.0232	–
	Infliximab biosimilar	853,247	14.2375	60,923
	Vedolizumab SC	875,495	14.3742	162,760
Inclusion of ustekinumab and tofacitinib	Conventional therapy	840,191	14.0232	–
	Vedolizumab SC	875,495	14.3742	100,582
Waning effect	Conventional therapy	840,337	14.0211	–
	Vedolizumab SC	875,807	14.3313	114,355
Societal perspective	Conventional therapy	1,106,134	14.0232	–
	Vedolizumab SC	1,132,949	14.3742	76,400
0% discount	Conventional therapy	1,184,052	19.4199	–
	Vedolizumab SC	1,218,616	19.7695	98,875
3% discount	Conventional therapy	624,884	10.6376	–
	Vedolizumab SC	660,535	10.9842	102,845

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor.

Note: Given the instability in the sponsor's probabilistic analysis, CADTH has reported sponsor's deterministic results. Only treatments that are on the efficiency frontier are reported.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table, as QALYs were rounded up to only four decimal places.

Table 13: Resource Use in the Sponsor's Submission

	Per 8-week resource use				One-time resource use	
	Remission	Response	Active UC	Post-surgery remission	Surgery	Post-surgery complications
Gastroenterologist	0.18	0.57	0.96	1.17	1.0	4.5
Dietician	0	0	0.03	0.05	0	0
IBD nurse	0.5	1	2	2	1	0.5
Psychologist	0	0	0.05	0.05	0	0
Blood test	0.32	0.57	0.96	1.17	1.00	1
Colonoscopy	0.04	0.08	0.4	0.25	1	1.13
Endoscopic biopsy	0.04	0.08	0.4	0.25	1	0.5
Colonic radiography	0	0	0.08	0	1	0.5
CT colonography	0.25	0.25	0.33	0	1	0.5
Hospitalization	0	0	0.2	0	0.5	0.5
Surgical procedure	0	0	0	0	1	0.5
Pouchitis treatment	0	0	0	0	0	1

CT = computed tomography; IBD = inflammatory bowel disease; UC = ulcerative colitis.

Appendix 4: CADTH Detailed Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 14: Summary of the Stepped Analysis of the CADTH Reanalysis Results in the Anti–TNF Alpha Naive Subgroup (Deterministic)

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)[a]
Sponsor's base case	Conventional therapy	837,313	14.0675	–
	Vedolizumab SC	874,017	14.4170	$105,042
	Vedolizumab IV	876,118	14.4298	$163,515
	Golimumab	874,131	14.2213	Dominated by vedolizumab SC
	Infliximab biosimilar	875,464	14.3020	Dominated by vedolizumab SC
	Adalimumab	883,941	14.1998	Dominated by vedolizumab SC, golimumab, infliximab biosimilar, and vedolizumab IV
Sponsor's corrected base case	Conventional therapy	837,414	14.0675	–
	Vedolizumab SC	874,110	14.4170	$105,021
	Vedolizumab IV	876,210	14.4298	$163,482
	Adalimumab	872,266	14.1998	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	875,559	14.3020	Dominated by vedolizumab SC
	Golimumab	877,332	14.2213	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
CADTH reanalysis 1: 20-year risk of surgery data[16]	Conventional therapy	823,532	13.8883	–
	Vedolizumab SC	861,109	14.2503	$103,815
	Vedolizumab IV	863,261	14.2639	$158,550
	Adalimumab	859,027	14.0296	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	862,401	14.1331	Dominated by vedolizumab SC
	Golimumab	864,151	14.0519	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
CADTH reanalysis 2: Suzuki et al. (2012) post-surgery complication rates	Conventional therapy	762,210	14.1021	–
	Vedolizumab SC	804,339	14.4490	$121,436
	Vedolizumab IV	806,752	14.4617	$189,907
	Adalimumab	800,977	14.2325	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	804,826	14.3345	Dominated by vedolizumab SC
	Golimumab	806,408	14.2538	Dominated by vedolizumab SC and infliximab biosimilar

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)[a]
CADTH reanalysis 3: Treating surgery and post-surgery complications as one-time costs	Conventional therapy	747,756	14.0675	–
	Vedolizumab SC	790,489	14.4170	$122,298
	Vedolizumab IV	792,939	14.4298	$190,640
	Adalimumab	786,948	14.1998	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	790,860	14.3020	Dominated by vedolizumab SC
	Golimumab	792,419	14.2213	Dominated by vedolizumab SC and infliximab biosimilar
CADTH reanalysis 4: Updated resource use	Conventional therapy	434,645	14.0675	–
	Vedolizumab SC	483,201	14.4170	$138,964
	Vedolizumab IV	485,991	14.4298	$217,098
	Adalimumab	475,032	14.1998	Extendedly dominated by conventional therapy and vedolizumab SC
	Golimumab	480,997	14.2213	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	481,522	14.3020	Extendedly dominated by conventional therapy and vedolizumab SC
CADTH reanalysis 5: No dose escalation or loss and regaining of response	Conventional therapy	837,414	14.0675	–
	Infliximab biosimilar	849,633	14.3332	$46,000
	Vedolizumab IV	876,210	14.4298	$275,043
	Adalimumab	872,266	14.1998	Dominated by infliximab biosimilar
	Vedolizumab SC	874,110	14.4170	Extendedly dominated by conventional therapy and infliximab biosimilar
	Golimumab	877,245	14.2321	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
CADTH reanalysis 6: Include ustekinumab and tofacitinib as comparators	Conventional therapy	837,414	14.0675	–
	Vedolizumab SC	874,110	14.4170	$105,021
	Vedolizumab IV	876,210	14.4298	$163,482
	Adalimumab	872,266	14.1998	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	875,559	14.3020	Dominated by vedolizumab SC
	Golimumab	877,332	14.2213	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
	Tofacitinib	880,426	14.3309	Dominated by vedolizumab SC and vedolizumab IV
	Ustekinumab	923,820	14.2503	Dominated by vedolizumab SC, infliximab biosimilar, vedolizumab IV, and tofacitinib
CADTH base case Sponsor's corrected base case plus	Conventional therapy	374,548	13.9139	–
	Tofacitinib	414,415	14.3478	$91,883

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)[a]
reanalyses 1, 2, 3, 4, 5, and 6	Infliximab biosimilar	400,237	14.1890	Extendedly dominated by conventional therapy and tofacitinib
	Adalimumab	417,831	14.0538	Dominated by infliximab biosimilar and tofacitinib
	Golimumab	424,481	14.0871	Dominated by infliximab biosimilar and tofacitinib
	Vedolizumab SC	427,126	14.2740	Dominated by tofacitinib
	Vedolizumab IV	430,147	14.2875	Dominated by tofacitinib
	Ustekinumab	443,068	14.1600	Dominated by vedolizumab SC, infliximab biosimilar, vedolizumab IV, and tofacitinib

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table, as QALYs were rounded up to only four decimal places.

Table 15: Summary of the Stepped Analysis of the CADTH Reanalysis Results in the Anti–TNF Alpha Exposed Subgroup (Deterministic)

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)[a]
Sponsor's base case	Conventional therapy	853,160	13.8402	–
	Vedolizumab SC	882,686	14.1133	$108,090
	Infliximab biosimilar	882,628	13.9290	Extendedly dominated by conventional therapy and vedolizumab SC
	Golimumab	883,029	13.8981	Dominated by vedolizumab SC and infliximab biosimilar
	Vedolizumab IV	884,875	14.0367	Dominated by vedolizumab SC
	Adalimumab	890,502	13.8741	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
Sponsor's corrected base case	Conventional therapy	853,264	13.8402	–
	Vedolizumab SC	882,783	14.1133	$108,061
	Adalimumab	881,656	13.8741	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	882,726	13.9290	Extendedly dominated by conventional therapy and vedolizumab SC
	Vedolizumab IV	884,972	14.0367	Dominated by vedolizumab SC
	Golimumab	886,233	13.8981	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
CADTH reanalysis 1: 20-year risk of surgery data	Conventional therapy	838,953	13.6543	–
	Vedolizumab SC	869,419	13.9411	$106,256
	Adalimumab	868,015	13.6977	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	869,121	13.7532	Extendedly dominated by conventional therapy and vedolizumab SC
	Vedolizumab IV	871,516	13.8631	Dominated by vedolizumab SC

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)[a]
	Golimumab	872,621	13.7221	Dominated by vedolizumab SC, infliximab biosimilar SC, and vedolizumab IV
CADTH reanalysis 2: Suzuki et al. post-surgery complication rates	Conventional therapy	775,271	13.8760	–
	Vedolizumab SC	810,636	14.1465	$130,752
	Adalimumab	807,746	13.9080	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	809,069	13.9628	Extendedly dominated by conventional therapy and vedolizumab SC
	Vedolizumab IV	812,254	14.0701	Dominated by vedolizumab SC
	Golimumab	812,520	13.9319	Dominated by vedolizumab SC and infliximab biosimilar
CADTH reanalysis 3: Treating surgery and post-surgery complications as one-time costs	Conventional therapy	760,507	13.8402	–
	Vedolizumab SC	796,515	14.1133	$131,818
	Adalimumab	793,419	13.8741	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	794,770	13.9390	Extendedly dominated by conventional therapy and vedolizumab SC
	Vedolizumab IV	798,064	14.0367	Dominated by vedolizumab SC
	Golimumab	798,214	13.8981	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
CADTH reanalysis 4: Updated resource use	Conventional therapy	442,229	13.8402	–
	Vedolizumab SC	482,083	14.1133	$145,900
	Adalimumab	473,568	13.8741	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	476,668	13.9290	Extendedly dominated by conventional therapy and vedolizumab SC
	Golimumab	479,102	13.8981	Dominated by infliximab biosimilar
	Vedolizumab IV	482,138	14.0367	Dominated by vedolizumab SC
CADTH reanalysis 5: No dose escalation	Conventional therapy	853,264	13.8402	–
	Vedolizumab SC	882,783	14.1133	$108,061
	Infliximab biosimilar	865,435	13.9457	Extendedly dominated by conventional therapy and vedolizumab SC
	Adalimumab	881,656	13.8741	Dominated by infliximab biosimilar
	Vedolizumab IV	884,972	14.0367	Dominated by vedolizumab SC
	Golimumab	886,183	13.9038	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
CADTH reanalysis 6: Include ustekinumab and	Conventional therapy	853,264	13.8402	–
	Vedolizumab SC	882,783	14.1133	$108,061

Stepped analysis	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALYs)[a]
tofacitinib as comparators	Adalimumab	881,656	13.8741	Extendedly dominated by conventional therapy and vedolizumab SC
	Infliximab biosimilar	882,726	13.9290	Extendedly dominated by conventional therapy and vedolizumab SC
	Vedolizumab IV	884,972	14.0367	Dominated by vedolizumab SC
	Golimumab	886,233	13.8981	Dominated by vedolizumab SC, infliximab biosimilar, and vedolizumab IV
	Tofacitinib	888,319	14.0731	Dominated by vedolizumab SC
	Ustekinumab	919,807	13.9271	Dominated by vedolizumab SC, infliximab biosimilar, vedolizumab IV, and tofacitinib
CADTH base case: Sponsor's corrected base case plus reanalyses 1, 2, 3, 4, 5, and 6	Conventional therapy	380,078	13.6809	–
	Tofacitinib	412,396	13.9553	$117,761
	Vedolizumab SC	424,256	13.9656	$1,152,959
	Infliximab biosimilar	401,230	13.7954	Extendedly dominated by conventional therapy and tofacitinib
	Adalimumab	414,434	13.7228	Dominated by infliximab biosimilar and tofacitinib
	Golimumab	420,340	13.7530	Dominated by infliximab biosimilar and tofacitinib
	Vedolizumab IV	423,884	13.8878	Dominated by tofacitinib
	Ustekinumab	432,871	13.8038	Dominated by vedolizumab SC, vedolizumab IV, and tofacitinib

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table, as QALYs were rounded up to only four decimal places.

Detailed Results of the CADTH Base Case

Table 16: Disaggregated Summary of CADTH's Economic Evaluation Results in the Anti–TNF Alpha Naive Population (Deterministic)

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
Discounted life-years[b]					
Conventional therapy	Total	31.76	–	–	–
Tofacitinib	Total	31.77	0.00	0.00	–
Vedolizumab SC	Total	31.77	0.00	–	–
Adalimumab SC	Total	31.77	0.00	–	–
Golimumab SC	Total	31.77	0.00	–	–
Infliximab biosimilar	Total	31.77	0.00	–	–
Vedolizumab IV	Total	31.77	0.00	–	–
Ustekinumab	Total	31.77	0.00	–	–

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
Discounted QALYs					
Conventional therapy	Response	0.59	–	–	–
	Remission	0.24	–	–	–
	Active UC	11.85	–	–	–
	Surgery	0.06	–	–	–
	Post-surgery remission	1.17	–	–	–
	Post-surgery complication	0.05	–	–	–
	Disutilities	−0.05	–	–	–
	Total	13.91	–	–	–
Vedolizumab SC	Response	0.80	0.21	–	–
	Remission	0.81	0.57	–	–
	Active UC	11.52	−0.32	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.08	−0.09	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.04	0.00	–	–
	Total	14.27	0.36	–	–
Adalimumab	Response	0.71	0.12	–	–
	Remission	0.47	0.23	–	–
	Active UC	11.72	−0.13	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.10	−0.06	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.05	−0.01	–	–
	Total	14.05	0.14	–	–
Golimumab	Response	0.73	0.14	–	–
	Remission	0.53	0.29	–	–
	Active UC	11.68	−0.17	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.10	−0.07	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.06	−0.01	–	–
	Total	14.09	0.17	–	–
Infliximab biosimilar	Response	0.77	0.18	–	–
	Remission	0.71	0.47	–	–

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
	Active UC	11.58	−0.27	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.09	−0.08	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.06	−0.02	–	–
	Total	14.19	0.28	–	–
Vedolizumab IV	Response	0.80	0.21	–	–
	Remission	0.86	0.61	–	–
	Active UC	11.50	−0.34	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.08	−0.09	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.05	−0.01	–	–
	Total	14.29	0.37	–	–
Ustekinumab	Response	0.76	0.17	–	–
	Remission	0.61	0.37	–	–
	Active UC	11.63	−0.22	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.10	−0.07	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.04	0.00	–	–
	Total	14.16	0.25	–	–
Tofacitinib	Response	0.79	0.20	0.20	45.17%
	Remission	0.98	0.74	0.74	170.57%
	Active UC	11.46	−0.39	−0.39	−89.83%
	Surgery	0.06	0.00	0.00	−0.76%
	Post-surgery remission	1.07	−0.10	−0.10	−23.13%
	Post-surgery complication	0.05	0.00	0.00	−1.01%
	Disutilities	−0.05	0.00	0.00	−1.01%
	Total	14.35	0.43	0.43	100%
Discounted costs					
Conventional therapy	Biologic therapy	$0	–	–	–
	Disease management cost (on treatment)	$363,555	–	–	–

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
	Surgery	$2,216	–	–	–
	Post-surgery complications	$1,048	–	–	–
	Post-surgery remission	$2,364	–	–	–
	Adverse events	$5,365	–	–	–
	Total	$374,548	–	–	–
Vedolizumab SC	Biologic therapy	$62,380	$62,380	–	–
	Disease management cost (on treatment)	$354,352	−$9,203	–	–
	Surgery	$2,113	−$103	–	–
	Post-surgery complications	$972	−$77	–	–
	Post-surgery remission	$2,191	−$173	–	–
	Adverse events	$5,118	−$247	–	–
	Total	$427,126	$52,577	–	–
Adalimumab	Biologic therapy	$47,084	$47,084	–	–
	Disease management cost (on treatment)	$359,275	−$4,280	–	–
	Surgery	$2,143	−$73	–	–
	Post-surgery complications	$993	−$55	–	–
	Post-surgery remission	$2,239	−$125	–	–
	Adverse events	$6,096	$730	–	–
	Total	$417,831	$43,282	–	–
Golimumab	Biologic therapy	$54,316	$54,316	–	–
	Disease management cost (on treatment)	$358,356	−$5,199	–	–
	Surgery	$2,133	−$83	–	–
	Post-surgery complications	$986	−$62	–	–
	Post-surgery remission	$2,223	−$141	–	–
	Adverse events	$6,466	$1,101	–	–
	Total	$424,481	$49,933	–	–
Infliximab biosimilar	Biologic therapy	$33,167	$33,167	–	–
	Disease management cost (on treatment)	$355,828	−$7,726	–	–
	Surgery	$2,125	−$91	–	–

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
	Post-surgery complications	$980	−$68	–	–
	Post-surgery remission	$2,210	−$154	–	–
	Adverse events	$5,927	$562	–	–
	Total	$400,237	$25,688	–	–
Vedolizumab IV	Biologic therapy	$65,626	$65,626	–	–
	Disease management cost (on treatment)	$353,858	−$9,697	–	–
	Surgery	$2,106	−$110	–	–
	Post-surgery complications	$967	−$81	–	–
	Post-surgery remission	$2,181	−$183	–	–
	Adverse events	$5,408	$43	–	–
	Total	$430,147	$55,599	–	–
Ustekinumab	Biologic therapy	$75,775	$75,775	–	–
	Disease management cost (on treatment)	$357,006	−$6,549	–	–
	Surgery	$2,132	−$84	–	–
	Post-surgery complications	$986	−$63	–	–
	Post-surgery remission	$2,222	−$142	–	–
	Adverse events	$4,948	−$418	–	–
	Total	$443,068	$68,520	–	–
Tofacitinib	Biologic therapy	$51,598	$51,598	$51,598	129%
	Disease management cost (on treatment)	$352,636	−$10,919	−$10,919	−27.39%
	Surgery	$2,093	−$123	−$123	−0.31%
	Post-surgery complications	$958	−$90	−$90	−0.23%
	Post-surgery remission	$2,161	−$203	−$203	−0.51%
	Adverse events	$4,970	−$395	−$395	−0.99%
	Total	$414,415	$39,866	$39,866	100%

Treatment	ICER versus conventional therapy	Sequential ICER ($)
Conventional therapy	–	–
Tofacitinib	$91,883	$91,883 versus conventional therapy
Vedolizumab SC	$146,005	Dominated by tofacitinib
Adalimumab	$309,364	Dominated by infliximab biosimilar and tofacitinib
Golimumab	$288,376	Dominated by infliximab biosimilar and tofacitinib
Infliximab biosimilar	$93,363	Extendedly dominated by conventional therapy and tofacitinib
Vedolizumab IV	$148,831	Dominated by tofacitinib
Ustekinumab	$278,476	Dominated by vedolizumab SC, infliximab biosimilar, vedolizumab IV, and tofacitinib

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis.

[a] Percentage of total incremental (e.g., if total incremental QALY is 0.36 and incremental QALY in response state is 0.21, percentage of total is 0.21 ÷ 0.36 = 57.73%).

[b] Given biologics do not impact mortality, there are no expected difference in life-years between treatments.

Table 17: Disaggregated Summary of CADTH's Economic Evaluation Results in the Anti–TNF Alpha Exposed Population

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
Discounted life-years[b]					
Conventional therapy	Total	31.76	–	–	–
Tofacitinib	Total	31.77	0.00	0.01	–
Vedolizumab SC	Total	31.77	0.00	0.00	–
Adalimumab	Total	31.76	0.00	–	–
Golimumab	Total	31.76	0.00	–	–
Infliximab biosimilar	Total	31.76	0.00	–	–
Vedolizumab IV	Total	31.77	0.00	–	–
Ustekinumab	Total	31.76	0.00	–	–
Discounted QALYs					
Conventional therapy	Response	0.28	–	–	–
	Remission	0.04	–	–	–
	Active UC	12.08	–	–	–
	Surgery	0.06	–	–	–
	Post-surgery remission	1.21	–	–	–
	Post-surgery complication	0.05	–	–	–
	Disutilities	−0.04	–	–	–
	Total	13.68	–	–	–
Vedolizumab SC	Response	0.55	0.27	−0.09	−919.42%
	Remission	0.41	0.37	0.10	998.70%

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
	Active UC	11.82	−0.27	0.01	92.10%
	Surgery	0.06	0.00	0.00	−3.77%
	Post-surgery remission	1.12	−0.09	−0.01	−106.18%
	Post-surgery complication	0.05	0.00	0.00	−4.65%
	Disutilities	−0.04	0.00	0.00	43.22%
	Total	13.97	0.28	0.01	100.00%
Adalimumab	Response	0.38	0.10	–	–
	Remission	0.09	0.06	–	–
	Active UC	12.04	−0.04	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.15	−0.06	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.05	0.00	–	–
	Total	13.72	0.04	–	–
Golimumab	Response	0.42	0.14	–	–
	Remission	0.13	0.09	–	–
	Active UC	12.01	−0.08	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.14	−0.07	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.06	−0.01	–	–
	Total	13.75	0.07	–	–
Infliximab biosimilar	Response	0.48	0.20	–	–
	Remission	0.16	0.13	–	–
	Active UC	11.96	−0.12	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.14	−0.07	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.06	−0.01	–	–
	Total	13.80	0.11	–	–
Vedolizumab IV	Response	0.52	0.24	–	–
	Remission	0.30	0.26	–	–
	Active UC	11.88	−0.20	–	–
	Surgery	0.06	0.00	–	–

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
	Post-surgery remission	1.13	−0.08	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.05	−0.01	–	–
	Total	13.89	0.21	–	–
Ustekinumab	Response	0.47	0.19	–	–
	Remission	0.16	0.12	–	–
	Active UC	11.97	−0.12	–	–
	Surgery	0.06	0.00	–	–
	Post-surgery remission	1.14	−0.07	–	–
	Post-surgery complication	0.05	0.00	–	–
	Disutilities	−0.04	0.00	–	–
	Total	13.80	0.12	–	–
Tofacitinib	Response	0.65	0.37	0.37	134.00%
	Remission	0.31	0.27	0.27	98.96%
	Active UC	11.81	−0.27	−0.27	−100.03%
	Surgery	0.06	0.00	0.00	−0.94%
	Post-surgery remission	1.13	−0.08	−0.08	−29.47%
	Post-surgery complication	0.05	0.00	0.00	−1.29%
	Disutilities	−0.05	0.00	0.00	−1.24%
	Total	13.96	0.27	0.27	100.00%
Discounted costs ($)					
Conventional therapy	Biologic therapy	$0	–	–	–
	Disease management cost (on treatment)	$368,916	–	–	–
	Surgery	$2,269	–	–	–
	Post-surgery complications	$1,088	–	–	–
	Post-surgery remission	$2,453	–	–	–
	Adverse events	$5,352	–	–	–
	Total	$380,078	–	–	–
Vedolizumab SC	Biologic therapy	$52,077	$52,077	$11,672.30	98%
	Disease management cost (on treatment)	$361,589	−$7,327	$121.32	1.02%
	Surgery	$2,159	−$110	−$14.45	−0.12%

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
	Post-surgery complications	$1,005	−$82	−$9.81	−0.08%
	Post-surgery remission	$2,267	−$186	−$22.14	−0.19%
	Adverse events	$5,159	−$193	$112.42	0.95%
	Total	$424,256	$44,178	$11,859.63	100.00%
Adalimumab	Biologic therapy	$35,782	$35,782	–	–
	Disease management cost (on treatment)	$367,201	−$1,715	–	–
	Surgery	$2,194	−$75	–	–
	Post-surgery complications	$1,030	−$58	–	–
	Post-surgery remission	$2,323	−$130	–	–
	Adverse events	$5,903	$552	–	–
	Total	$414,434	$34,356	–	–
Golimumab	Biologic therapy	$42,293	$42,293	–	–
	Disease management cost (on treatment)	$366,333	−$2,583	–	–
	Surgery	$2,188	−$81	–	–
	Post-surgery complications	$1,026	−$61	–	–
	Post-surgery remission	$2,314	−$139	–	–
	Adverse events	$6,185	$833	–	–
	Total	$420,340	$40,262	–	–
Infliximab biosimilar	Biologic therapy	$24,772	$24,772	–	–
	Disease management cost (on treatment)	$365,172	−$3,744	–	–
	Surgery	$2,185	−$84	–	–
	Post-surgery complications	$1,024	−$64	–	–
	Post-surgery remission	$2,308	−$145	–	–
	Adverse events	$5,769	$417	–	–
	Total	$401,230	$21,153	–	–
Vedolizumab IV	Biologic therapy	$49,803	$49,803	–	–
	Disease management cost (on treatment)	$363,224	−$5,692	–	–
	Surgery	$2,170	−$99	–	–

Treatment	Component	Value	Incremental (versus conventional therapy)	Incremental (sequential)	Percentage of total incremental (sequential)[a]
	Post-surgery complications	$1,013	−$74	–	–
	Post-surgery remission	$2,285	−$168	–	–
	Adverse events	$5,388	$37	–	–
	Total	$423,884	$43,807	–	–
Ustekinumab	Biologic therapy	$56,935	$56,935	–	–
	Disease management cost (on treatment)	$365,366	−$3,550	–	–
	Surgery	$2,188	−$81	–	–
	Post-surgery complications	$1,026	−$62	–	–
	Post-surgery remission	$2,314	−$139	–	–
	Adverse events	$5,042	−$310	–	–
	Total	$432,871	$52,793	–	–
Tofacitinib	Biologic therapy	$40,405	$40,405	$40,405	125.02%
	Disease management cost (on treatment)	$361,468	−$7,448	−$7,448	−23.05%
	Surgery	$2,173	−$96	−$96	−0.30%
	Post-surgery complications	$1,015	−$73	−$73	−0.22%
	Post-surgery remission	$2,289	−$164	−$164	−0.51%
	Adverse events	$5,047	−$305	−$305	−0.94%
	Total	$412,396	$32,319	$32,319	100.00%

Treatment	ICER versus conventional therapy ($)	Sequential ICER ($)
Conventional therapy	–	–
Tofacitinib	$117,761	$117,761 versus conventional therapy
Vedolizumab SC	$155,159	$1,152,959 versus tofacitinib
Adalimumab	$818,357	Dominated by infliximab biosimilar and tofacitinib
Golimumab	$557,777	Dominated by infliximab biosimilar and tofacitinib
Infliximab biosimilar	$184,703	Extendedly dominated by conventional therapy and tofacitinib
Vedolizumab IV	$211,719	Dominated by tofacitinib
Ustekinumab	$429,386	Dominated by vedolizumab SC, vedolizumab IV, and tofacitinib

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis.

[a] Percentage of total incremental (e.g., if total incremental QALY is 0.36 and incremental QALY in response state is 0.21, % of total is 0.21/0.36 = 57.73%%).

[b] Given that biologics do not impact mortality, there are no expected difference in life-years between the treatments.

Table 18: Resource Use in the CADTH Reanalyses

	Per 8-week resource use				One-time resource use	
	Remission	Response	Active UC	Post-surgery remission	Surgery	Post-surgery complications
Gastroenterologist	0.31	0.69	1.00	0.15	1	3.0
Dietician	0	0	0.05	0.02	0	0
IBD nurse	0.0	0	0	0	0	0
Psychologist	0	0	0	0	0	0
Blood test	0.50	0.60	1.00	0.23	1.00	3.25
Colonoscopy	0.08	0.23	0.3	0.04	1	1.50
Endoscopic biopsy	0.04	0.08	0.4	0.25	1	0.5
Colonic radiography	0	0	0.08	0	1	0.5
CT colonography	0	0	0	0	0	0
Hospitalization	0	0	0.1	0	0	0
Surgical procedure	0	0	0	0	1	0.5
Pouchitis treatment	0	0	0	0	0	1

CT = computed tomography; IBD = inflammatory bowel disease; UC = ulcerative colitis.

Scenario Analyses

Table 19: Scenario Analysis With Loss and Regaining of Response Applied in the Anti–TNF Alpha Naive Population

Drug	Total costs ($)	Total QALYs	ICER versus conventional therapy ($)	Sequential ICER[a]
Conventional therapy	374,548	13.91	–	–
Infliximab biosimilar	399,922	14.16	104,322	$104,322 versus conventional therapy
Vedolizumab IV	430,147	14.29	148,831	$231,881 versus infliximab biosimilar
Adalimumab	417,831	14.05	309,364	Dominated by infliximab biosimilar and tofacitinib
Golimumab	424,065	14.08	305,530	Dominated by infliximab biosimilar and tofacitinib
Vedolizumab SC	427,126	14.27	146,005	Extendedly dominated by infliximab biosimilar and vedolizumab IV
Ustekinumab	439,633	14.10	341,999	Dominated by vedolizumab SC, infliximab biosimilar, vedolizumab IV, and tofacitinib
Tofacitinib	411,150	14.19	134,159	Extendedly dominated by infliximab biosimilar and vedolizumab IV

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor.

Note: Given the instability in the sponsor's probabilistic analysis, CADTH has reported the sponsor's deterministic results. Only treatments that are on the efficiency frontier are reported. Detailed results, including treatments that are not on the cost-effectiveness efficiency frontier, can be found in Appendix 3.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table, as QALYs were rounded up to only four decimal places.

Table 20: Scenario Analysis With Loss and Regaining of Response Applied in the Anti–TNF Alpha Exposed Population

Drug	Total costs ($)	Total QALYs	ICER versus conventional therapy ($)	Sequential ICER[a]
Conventional therapy	380,078	13.68	–	–
Tofacitinib	411,615	13.92	130,156	$130,156 versus conventional therapy
Vedolizumab SC	424,256	13.97	$155,159	$297,961 versus tofacitinib
Infliximab biosimilar	401,050	13.78	215,444	Extendedly dominated by conventional therapy and tofacitinib
Adalimumab	414,434	13.72	818,357	Dominated by vedolizumab SC, infliximab biosimilar, and tofacitinib
Golimumab	420,111	13.75	603,560	Dominated by infliximab biosimilar and tofacitinib
Vedolizumab IV	423,884	13.89	211,719	Dominated by tofacitinib
Ustekinumab	431,063	13.78	537,359	Dominated by vedolizumab SC, infliximab biosimilar, vedolizumab IV, and tofacitinib

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = subcutaneous; TNF = tumour necrosis factor.

Note: Given the instability in the sponsor's probabilistic analysis, CADTH has reported the sponsor's deterministic results. Only treatments that are on the efficiency frontier are reported. Detailed results, including treatments that are not on the cost-effectiveness efficiency frontier, can be found in Appendix 3.

[a] Given the small QALY differences between treatments, the sequential ICER reported here may be different from the ICER that would have been calculated based on the reported total costs and QALYs within this table as, QALYs were rounded up to only four decimal places.

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