Common Drug Review
Pharmacoeconomic Review Report

April 2016

Drug	adalimumab (Humira)
Indication	Treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy including corticosteroids, azathioprine and/or 6-mercaptopurine (6-MP) or who are intolerant to such therapies.
Listing request	As per indication
Dosage form(s)	40 mg in 0.8 mL sterile solution for subcutaneous injection
NOC date	21 November 2013
Manufacturer	AbbVie Corporation

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

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ABBREVIATIONS

CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CEAC	cost-effectiveness acceptability curve
CMA	cost-minimization analysis
CUA	cost-utility analysis
DSA	deterministic sensitivity analysis
HAS	Haute Autorité de Santé (France)
ICUR	incremental cost-utility ratio
NICE	National Institute for Health and Care Excellence (UK)
NMA	network meta-analysis
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SOC	standard of care
TNF	tumour necrosis factor
UC	ulcerative colitis
WTP	willingness-to-pay

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Adalimumab Solution for SC Injection
Study Question	The objective of this study was to compare the cost-utility of adding ADA to SOC vs. SOC alone for the treatment of patients with moderately to severely active UC who have had an inadequate response to SOC. In addition, a CMA was conducted to evaluate total cost differences between the ADA + SOC strategy versus IFX + SOC, and versus GOL + SOC
Type of Economic Evaluation	• Primary: CUA (vs. SOC) • Secondary: CMA (vs. GOL and IFX)
Target Population	Patients with moderately to severely active UC who have an inadequate response to SOC. Three subgroup analyses: • anti-TNF alpha naive • early responders (after induction) • early responders who are anti-TNF alpha naive

Treatment	• Adalimumab in combination with SOC:
	  ○ Induction: 160 mg at week 0 and 80 mg at week 2
	  ○ Maintenance: 40 mg EOW starting from week 4

Outcome	QALYs

Comparators	Primary comparator:
	• SOC alone (anti-inflammatory drugs [e.g., aminosalicylates, corticosteroids] and immunosuppressants [e.g., azathioprine, 6-MP, and cyclosporine])
	Secondary comparators:
	• IFX in combination with SOC
	  ○ Induction: 5 mg/kg at weeks 0, 2, and 6
	  ○ Maintenance: 5 mg/kg every eight weeks starting at week 14
	• GOL in combination with SOC
	  ○ Induction: 200 mg at week 0 and 100 mg at week 2
	  ○ Maintenance: 50 mg every four weeks from week 6

Perspective	Canadian publicly funded health care system
Time Horizon	10 years
Results for Base Case	CUA comparing ADA + SOC vs. SOC alone: • ICUR = $76,817 per QALY gained for the full population • ICUR = $79,066 per QALY gained for the anti-TNF alpha naive group • ICUR = $65,154 per QALY gained for the early responder group • ICUR = $69,372 per QALY gained for the group who are early responders and anti-TNF alpha naive CMA comparing ADA + SOC vs. IFX + SOC and vs. GOL + SOC: ADA is cost-saving compared with IFX and GOL.
Key Limitations	CDR identified the following key limitations: • Substantial uncertainty with the utility estimates used, which may favour ADA + SOC. • Uncertainty in dose escalation rate for the biologics, which may be underestimated for all treatments. Although this is likely to favour ADA + SOC (CUA) and IFX (CMA), this does not change the overall conclusions of the analyses. • No consideration of treatment waning. CDR could not test the impact of this limitation.

Drug Product	Adalimumab Solution for SC Injection
	• There is some uncertainty regarding the comparative effectiveness of ADA and other biologics and the manufacturer's conclusion of equal safety and efficacy of the biologics. CDR could not test varying this assumption.
CDR Estimates	• All CDR reanalyses were run without an 8% markup included in the manufacturer's analysis (which reduced the manufacturer's base-case ICUR to $69,819). • For ADA + SOC vs. SOC alone, CDR reanalyses indicated an ICUR ranging from $67,000 per QALY to $130,000 per QALY. This range is driven by the utility values used for the model health states, mostly the utility applied to the moderate to severe UC disease health state. • For ADA + SOC vs. biologic + SOC, CDR reanalyses found ADA to be cost-saving compared with GOL and IFX, where an assumption of equal efficacy and harms holds.

ADA = adalimumab; CDEC = CADTH Canadian Drug Expert Committee; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; CUA = cost-utility analysis; EOW = every other week; GOL = golimumab; ICUR = incremental cost-utility ratio; IFX = infliximab; QALY = quality-adjusted life-year; SC = subcutaneous; SOC = standard of care; TNF = tumour necrosis factor; UC = ulcerative colitis; vs. = versus.

EXECUTIVE SUMMARY

Background

Adalimumab (Humira) is an anti-tumour necrosis factor alpha (TNF alpha), available as a syringe of 40 mg/0.8 mL solution for subcutaneous injection at a unit price of $740.36 per syringe. The current review of adalimumab is for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy including corticosteroids, azathioprine and/or 6-mercaptopurine (6-MP), or who are intolerant to such therapies.[1]

Treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy including corticosteroids, azathioprine and/or 6-mercaptopurine (6-MP) or who are intolerant to such therapies.

Adalimumab has previously been reviewed by the CADTH Common Drug Review (CDR) for rheumatoid arthritis,[2] psoriatic arthritis,[3] ankylosing spondylitis,[4] Crohn disease,[5] psoriasis,[6] and polyarticular juvenile idiopathic arthritis.[7] For each of the above indications, the Canadian Drug Expert Committee (CDEC) final recommendation was that adalimumab be listed with criteria or conditions. CDR has also previously reviewed adalimumab for moderate to severe UC; however, the manufacturer withdrew from the process during the embargo period.[8] CDR also reviewed infliximab, golimumab, and most recently, vedolizumab, for moderate to severe UC. CDEC recommended that infliximab not be listed (although it can be accessed through restricted or special access in some jurisdictions), that golimumab not be listed at the submitted price,[9,10] and that vedolizumab be listed with criteria or conditions.[11]

When comparing adalimumab + standard of care (SOC) with SOC alone in patients with moderately to severely active UC, the manufacturer reported that adalimumab was associated with an incremental cost-utility ratio (ICUR) of $76,817 per quality-adjusted life-year (QALY). When excluding markups on drug costs (e.g., 8%), the ICUR was reduced to $69,819 per QALY. The manufacturer also undertook a secondary analysis comparing adalimumab + SOC with infliximab + SOC and golimumab + SOC individually, assuming equivalent efficacy and safety. The manufacturer reported that over a 10-year time horizon, considering only drug costs and excluding markups, adalimumab + SOC was cost-saving compared with infliximab + SOC and with golimumab + SOC: savings of $33,026 versus infliximab and of $5,433 versus golimumab were calculated.

Summary of identified limitations and key results

CDR identified the following limitations with the manufacturer's submission, which CDR was able to examine through an analysis of the manufacturer's economic model. CDR undertook a reanalysis of the manufacturer's base-case cost-utility analysis (CUA) and the secondary cost-minimization analysis (CMA) excluding drug markup costs.

For the CMA assessment presented by the manufacturer comparing adalimumab to infliximab and to golimumab, CDR identified uncertainty surrounding the potential wastage associated with infliximab and dose escalation for compared biologics. CDR also noted the impact of patient weight on the results for infliximab. CDR emphasized that the conclusions from the CMA are dependent on the assumption of equal efficacy and safety of the compared biologics. Under these conditions, CDR reanalyses concluded that adalimumab is cost-saving compared with infliximab and golimumab.

One other important issue for consideration was that in the period between when adalimumab was submitted and the time it was reviewed by CDEC, another treatment for UC — vedolizumab — received a recommendation of "list with clinical criteria and conditions" from CDEC. The comparative effectiveness of adalimumab compared with vedolizumab in patients with moderately to severely active UC is not known and could not be assessed by CDR. However, under an assumption of equal efficacy, safety, and usage, the use of adalimumab is likely cheaper than the use of vedolizumab based on the available drug costs.

CDR identified limitations for the CUA that were tested through one-way and multi-way reanalyses. Multi-way reanalyses of the CUA indicated that the ICUR for adalimumab + SOC compared with SOC alone ranged from $67,000 per QALY to $130,000 per QALY. One-way reanalyses found the results to be insensitive when addressing most limitations independently. The following limitations were identified for reanalysis after removing the 8% markup on drug costs applied by the manufacturer on their base-case analysis (resulting in an ICUR of $69,819 per QALY):

- Utility values identified by the manufacturer indicated a wide variance for utility scores, leading to uncertainty in determining appropriate values. CDR undertook reanalyses using values lower and higher than the manufacturer's base case. The model was sensitive to utility values used: ICUR ranged from $71,000 to $104,000 per QALY. CDR noted that these results were primarily driven by the utility value for the moderate to severe UC disease health states.
- Surgery rate was based on pooled data from three publications reporting rates of surgery in Europe, which were higher than those reported in a Canadian study identified by CDR (and verified by the CDR clinical expert consulted for this review). The model was not sensitive to this variation of the surgery rate (ICUR: $70,000 per QALY).
- The rate of dose escalation in ULTRA trials may differ from Canadian clinical practice based on feedback from the CDR clinical expert and an observational cohort study of adalimumab in UC patients. The model was not sensitive to changes in dose escalation rate (ICUR ranged from $67,000 to $73,000 per QALY).
- The cost per cycle for SOC was based on data from an infliximab trial. Data from ULTRA 2 indicated that the cost of SOC per cycle may be nearly twice what was assumed. The model was not sensitive to the cost of SOC (ICUR: $71,000 per QALY).
- The manufacturer assumed no biologic discontinuation between week 8 and week 104; however, the discontinuation rates in ULTRA 1 and ULTRA 2 suggested this was not appropriate. The model was not sensitive to the treatment discontinuation rate (ICUR: $75,000 per QALY).

CDR noted other limitations with the manufacturer's CUA model which were unable to be tested:

- No subgroup analysis was provided for patients with previous exposure to biologics. Subsequent use of biologics is likely to increase the costs associated with adalimumab and lead to a higher ICUR for adalimumab + SOC relative to SOC alone. This can be explained by the lower rate of responders in this subgroup compared with the response rate in patients with no prior exposure to biologic treatments.[12] Forty per cent of patients in ULTRA 2 had received treatment with an anti-TNF alpha in the five years leading up to the trial.
- The manufacturer did not include treatment waning in their analysis. Given the model structure, CDR was unable to undertake reanalyses to reliably test this assumption.

Conclusions

Although other biologic drugs may be reimbursed for UC in some Canadian jurisdictions, the availability of these drugs differs across the country. CDR found that despite several limitations that were identified

with the CMA, adalimumab may be cost-saving compared with infliximab and compared with golimumab. However, this conclusion is dependent on the assumption of equal safety and efficacy for these biologics in the treatment of UC. The comparative cost-effectiveness of adalimumab compared with vedolizumab in patients with moderately to severely active UC is not known and could not be assessed by CDR. However, under an assumption of equal efficacy, safety, and usage, the use of adalimumab is likely cheaper than the use of vedolizumab based on the available drug costs.

In jurisdictions where other biologic drugs are not available for use in UC, CDR suggests the ICUR for adalimumab + SOC compared with SOC alone may be between $67,000 per QALY and $130,000 per QALY. However CDR notes that some areas of uncertainty were unable to be tested, which may impact the results.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) to estimate the incremental cost per quality-adjusted life-year (QALY) gained for the adalimumab and standard of care (SOC) combination therapy versus SOC treatment alone in patients with ulcerative colitis (UC), from the perspective of Canada's publicly funded drug plans over a 10-year time horizon.[1] The manufacturer also presented a de facto cost-minimization analysis (CMA) of adalimumab + SOC compared with golimumab + SOC and infliximab + SOC; these regimens were included in the model under the assumption of equal efficacy and safety.

Three categories of health states were used in the manufacturer's Markov model of two-week cycles: pre-surgery, surgery, and post-surgery. The pre-surgery health states are based on disease severity: remission, mild, and moderate to severe, defined using full Mayo scores from ULTRA 2 and ULTRA 3, or partial Mayo scores in the event that full Mayo scores were not available. Surgery was a tunnel state into which patients could enter only from the moderate to severe state, stay for only one cycle, and not return to that state again. Four post-surgery health states were used based on surgical outcome: post-surgery without complication, post-surgery transient complication, post-surgery chronic complication, and surgery-related death.

Patients entered the model in the moderate to severe health state, and could transition between health states at the beginning of each model cycle (every two weeks) thereafter. Pre-surgery transition probabilities were estimated primarily from the ULTRA 2 trial and the ULTRA 3 extension trial for adalimumab + SOC and SOC alone, although as transitions from remission or mild state could not be derived based on the trial data, published literature was used for those estimations. Transition probabilities were estimated for four specific time periods in the model: week 0 to week 8, week 8 to week 52, week 52 to week 104, and week 104 to week 520. Dose escalation was incorporated into the model from week 8 onwards. The extension study (ULTRA 3) did not study SOC alone; therefore, data from the SOC group in the ULTRA 2 study were used as transition probabilities through the 10-year time horizon. The ULTRA 3 trial is ongoing, and the manufacturer used data directly from that study to determine transition probabilities up to week 292 in the model. Beyond that time point, a multinomial logit regression model was used to estimate transition probabilities to week 520. Although surgery data may have been available in the ULTRA trials, transitional probabilities in the surgery and post-surgery states were sourced from published literature reporting real-world data. Surgery rates were estimated based on a weighted average of surgery rates from three publications that have specifically reported the rate of surgery among moderate to severe UC patients.[13-15] The post-surgery transient complication rate was a US-based publication[16] and the rate of post-surgery death was based on a UK study.[17] A constant hazard assumption was applied to the post-surgery transitional probabilities.

Utility values for the health states were based on various sources from the published literature. Biologic drug costs were obtained from the Ontario Drug Benefit Formulary,[18] with total costs incorporating dosing schedules for the biologics based on product monographs,[19-21] an average body weight of 80 kg, and a 12.4% dose wastage rate.[22] Infusion costs were not considered as they are expected to be reimbursed by the manufacturer. SOC drug costs were calculated using a claims analysis of la Régie de l'assurance maladie du Québec (RAMQ) data. The medical costs for all pre-surgery states, the post-

surgery without complication state, and the post-surgery with chronic complication state were estimated based on a Canadian survey of specialists.[1] Unit costs for examinations and specialist consultation visits were obtained from the Ontario Schedule of Benefits,[23] Ontario Guide to Interdisciplinary Provider Compensation,[24] and Ontario Nurses Association (ONA) collective bargaining agreement.[25] Surgery costs were sourced from the Ontario Ministry of Health and Long-Term Care (MoHLTC),[23] while hospitalization costs were sourced from the Ontario Case Costing Initiative.[26] Medical costs for post-surgery transient complications were derived from published literature.[16] Hospitalization rates, surgery rates, and complication rates were sourced from the ULTRA 1 and ULTRA 2 trials and published literature. All costs were inflated using the health care component of the Canadian Consumer Price Index, and were exchange-rate adjusted to 2014 Canadian dollars.

Subgroup analyses were undertaken on responders at week 8, patients naive to anti-tumour necrosis factor (TNF) alpha drugs, and responders at week 8 who were naive to anti-TNF alpha drugs.

The manufacturer undertook deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) on both the primary base-case (CUA) and secondary base case (CMA).

2. MANUFACTURER'S BASE CASE

The manufacturer's primary base-case CUA of adalimumab + SOC versus SOC alone reported that over a 10-year time horizon, adalimumab + SOC was associated with a further 0.7374 QALY than SOC alone, but at an extra cost of $56,642. This resulted in an ICUR of $76,817 per QALY gained for adalimumab + SOC versus SOC alone (although this included an 8% markup). When the drug price markup was excluded, the incremental cost-utility ratio ICUR was reduced to $69,819.

The manufacturer's secondary base-case CMA of adalimumab + SOC versus golimumab + SOC and versus infliximab + SOC reported that over a 10-year time horizon, adalimumab + SOC was cost-saving compared with golimumab + SOC (–$5,878) and with infliximab + SOC (–$35,669). When the drug price markup was excluded, adalimumab was similarly cost-saving.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer reported that the DSA on the primary base-case CUA found the results of the model to be robust, with the ICURs ranging from $53,280 per QALY gained to $93,646 per QALY gained for adalimumab + SOC versus SOC alone. The results of the PSA indicated a mean (95% confidence interval [CI]) ICUR per QALY of $87,427 ($84,979 to $89,874). The cost-effectiveness acceptability curve (CEAC) indicated that at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained, there is a near 0% probability that adalimumab + SOC is cost-effective compared with SOC alone; however, approximately 80% of simulations were below the threshold of $100,000 per QALY gained, and 91% of them were below the $125,000 threshold.

The manufacturer reported that both the DSA and PSA on the secondary base-case CMA found that adalimumab + SOC continued to be cost-saving compared with the other regimens in all parameters tested.

The three subpopulation analyses undertaken by the manufacturer found similar results to the base-case analysis, with the ICURs ranging from $65,000 per QALY gained (for week 8 responders) to $79,000 per QALY gained (for anti-TNF alpha naive patients).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CDR identified the following limitations with the manufacturer's submission, for which CDR was able to test via reanalysis for the comparison of adalimumab + SOC versus the other biologics + SOC (CMA):

- **There is uncertainty surrounding the potential wastage associated with infliximab. The** manufacturer assumed dose wastage for infliximab to be 12.4% annually based on data from Rutgeerts et al.[22] The CDR clinical expert indicated that wastage was generally kept to a minimum, as the dose of infliximab could be managed to reduce wastage by rounding to the nearest full vial. CDR undertook reanalyses varying the levels of wastage from 0% to 20%.
- **Dose escalation is uncertain.** The manufacturer reported dose escalation based on data from the ULTRA trials. As previously noted, the CDR clinical expert indicated that a lower rate of dose escalation for adalimumab (15% to 17%) is generally seen in patients with Crohn disease, while a higher rate of dose escalation is seen with infliximab (30%); the clinical expert suggested these results may be extrapolated to UC. As previously noted, CDR also identified an observational study that reported dose escalation was required in 35% of adalimumab patients over a 13-month period. CDR undertook sensitivity analyses, testing dose escalation rates.[27]
- **Results of the CMA are impacted by patient weight.** CDR noted that as infliximab dosing is based on patient weight, it would be appropriate to test the model to determine the comparative costs based on both lower and higher patient weights than were used in the manufacturer's analysis.

CDR identified the following limitation for the comparison of adalimumab + SOC versus the other biologics + SOC (CMA), which was unable to be tested:

- **Uncertain comparative efficacy between adalimumab, infliximab, and golimumab.** CDR clinical review identified five network meta-analyses (NMAs) that assessed adalimumab, golimumab, infliximab, and vedolizumab (as well as SOC).[28-32] All NMAs supported the superiority of the biologics over placebo in the induction phase,[28-32] and most in the maintenance phase.[28-30,32] CDR clinical reviewers found that infliximab was favoured over adalimumab in the induction phase,[29,30,32] but that there was generally no difference between the treatments in the maintenance phase (one study did find a difference).[30] CDR noted that there were limitations with the conduct of the NMAs, which resulted in uncertainty with regard to the results. Thus, this uncertainty regarding the comparative efficacy of the biologic treatments renders uncertain the conclusion of the CMA comparing biologics, which is dependent of the assumption of their equal safety and efficacy.

CDR identified the following limitations with the manufacturer's submission, for which CDR was able to test via reanalysis for the comparison of adalimumab + SOC versus SOC alone (CUA):

- **There is substantial uncertainty with the utility estimates.** The manufacturer identified several utility values, which indicated a wide variance in utility scores. The manufacturer used values for pre-surgery states from a study reported in abstract form only.[33] The values for post-surgery states were based on utility estimates reported by Tsai et al.,[34] which were also sourced from a study reported only in abstract form.[35] Furthermore, the post-surgery states utility values used in the model do not match the values in the abstract. Additionally, the external validity of the association between the different health state utility values used in the manufacturer's base case was not demonstrated by the manufacturer. CDR undertook a sensitivity analysis using values higher and

lower than the manufacturer's base case to assess the volatility of the model results derived by varying this model component. CDR notes that the results of the model appear to be driven by the utility value for the moderate to severe UC disease health state.

- **Surgery rate may be overestimated.** The manufacturer's surgery rate (0.0044 per cycle, ~11% per year) was based on pooled data from three publications reporting rates of surgery in Europe.[13-15] CDR notes that a Canadian study is available, which reports the rate of colectomy as 3.6% at one year and 10.4% at 10 years.[36] The CDR clinical expert indicated the rate of surgery has decreased over recent years and is likely to be somewhere between 5% and the 11% used by the manufacturer. CDR undertook reanalyses using a lower surgery rate (0.0020 per cycle, ~5% per year).
- **Rate of dose escalation is uncertain.** The manufacturer considered rates of dose escalation as seen in the ULTRA trials. The CDR clinical expert indicated that dose escalation for adalimumab generally ranged from 15% to 17%, albeit in patients with Crohn disease. However, an observational cohort study of UC patients indicated that 35% of patients treated with adalimumab required dose escalation over 13 months.[27] Thus, CDR undertook reanalyses testing both lower and high dose escalation rates.
- **SOC costs may be underestimated.** The manufacturer used a cost per two-week cycle of approximately $27 (approximately $55 per month) for SOC. Data from ULTRA 2 indicates that approximately 93% of patients received some form of standard UC treatment at study baseline: either a corticosteroid (65%), 6-mercaptopurine (6-MP), or azathioprine (38%), or an aminosalicylate (66%). Assuming standard treatments and costs based on the Ontario Drug Benefit Formulary, the cost of SOC per cycle is approximately double that used by the manufacturer. CDR undertook reanalyses assuming a cost of $58 per cycle for SOC.
- **Treatment discontinuation between week 8 and week 104 was not considered.** The manufacturer assumed patients would not discontinue treatment between week 8 (end of induction period) and week 104. However, the discontinuation rate in ULTRA 1 and ULTRA 2 studies were 27% and 38% in the adalimumab arm, respectively, and 30% and 47% in the placebo arm, respectively. Thus, as performed by the manufacturer in sensitivity analyses, CDR applied discontinuation rates as part of the reanalyses.

CDR identified the following limitations for the comparison of adalimumab + SOC versus SOC alone (CUA), which were unable to be tested:

- **No subgroup analysis was provided for patients with previous exposure to biologics.** Subsequent use of biologics is likely to increase the costs associated with adalimumab and lead to a higher ICUR of adalimumab + SOC relative to SOC. This can be explained by a likely lower rate of responders in this subgroup compared with the response rate in patients with no prior exposure to biologic treatments.[12] Forty per cent of patients in ULTRA 2 had received treatment with an anti-TNF alpha in the five years leading up to the trial.
- **The manufacturer did not include treatment waning in its analysis.** Given the model structure, CDR was unable to undertake reanalyses to reliably test this assumption.

5. CADTH COMMON DRUG REVIEW REANALYSES

Based on the assumption that the efficacy and safety profile of adalimumab is equivalent to that of infliximab and golimumab, CDR reanalyses affecting biologic treatment costs found that using the presented model parameters, adalimumab was less costly than infliximab and golimumab over the 10-year time horizon in all CDR reanalyses.

For the CUA comparing adalimumab + SOC versus SOC alone, CDR undertook several one-way and multi-way reanalyses, where possible. The results indicated that the model was generally robust over the majority of the parameters able to be tested. CDR one-way sensitivity analyses found the ICUR for adalimumab + SOC compared with SOC alone ranged from $67,000 per QALY to $104,000 per QALY. CDR multi-way sensitivity analyses found the ICUR for adalimumab + SOC compared with SOC alone ranged from $67,000 per QALY to $130,000 per QALY.

CDR undertook a price reduction analysis using both the low- and high-end ICURs resulting from reanalyses, which found that a price reduction of between 20% and 53% was required for adalimumab to be cost-effective compared with SOC when used as an add-on to SOC (Table 2).

TABLE 2: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIOS

ICURs of Adalimumab for the Base Cases (vs. SOC)[a]			
Price of Adalimumab ($)	**Manufacturer ($/QALY)**	**CDR Lower Estimate ($/QALY)**	**CDR Upper Estimate ($/QALY)**
Submitted (740.36)	69,819	67,093	130,253
10% reduction (666.32)	61,072	58,930	114,830
20% reduction (592.29)	52,325	50,766	99,406
30% reduction (518.25)	43,578	42,603	83,983
40% reduction (444.22)	34,830	34,440	68,559
50% reduction (370.18)	26,083	26,276	53,136
60% reduction (296.14)	17,336	18,113	37,712
70% reduction (222.11)	8,588	9,950	22,288
80% reduction (148.07)	Dominant	1,787	6,865

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.
[a] Based on the drug prices with markup excluded.

6. ISSUES FOR CONSIDERATION

In the period between the time adalimumab was submitted and the time it was reviewed by the CADTH Canadian Drug Expert Committee (CDEC), another treatment for UC — vedolizumab — received a CDEC recommendation of "list with clinical criteria and conditions".

7. PATIENT INPUT

Input was received from two patient groups: Crohn's and Colitis Canada and the Gastrointestinal (GI) Society. These groups obtained information through the following means to support their submissions: telephone interviews, a 2011 national online survey, a questionnaire, one-to-one conversations, round tables, discussions with health care professionals, and Crohn's and Colitis Canada published reports.

Patient input indicated that symptoms of UC can affect patients' physical, emotional, and social well-being by causing anxiety and stress, limiting the places they can go, and the activities (including work) they can participate in. The patient groups noted there is a stigma related with UC, which is particularly problematic for children, as they rarely get to experience a "normal life."

Patient input reported that there are a limited number of treatment options for UC, fewer than for Crohn disease. Current treatment in patients with mild-to-moderate UC is aminosalicylates as first-line treatment; if remission is not achieved or their condition becomes worse, patients move on to immunosuppressants and/or steroids. Patients indicated that sustained remission/treatment response is more important than relieving any one symptom of UC. Biologic drugs are also available to some patients for the treatment of UC. Patients reported that, although they are associated with risk factors, biologics provide an important and preferred option before surgery (colectomy), after first- and second-line therapies have failed. Patients reported that drug coverage is a concern, given inequalities of access to biologics across Canada. They noted that although biologics are expensive, in the long run they may be less costly for society that the alternatives, considering health care expenses, surgeries, and hospital stays, as well as lost work productivity and long-term disability funding. Patient input noted that the use of adalimumab increases remission rates, enabling patients to return to work more quickly, and it is more administration-friendly as a self-injection that can be administered at home, potentially improving adherence. However, there was some apprehension regarding the cost of, and access to, adalimumab; some patients claimed they were deliberately misdiagnosed with Crohn disease to obtain access to the greater variety of biologic treatments unavailable in their province or territory for UC.

8. CONCLUSIONS

Although other biologic drugs may be reimbursed for UC in some Canadian jurisdictions, their availability differs across the country. CDR found that despite several limitations that were identified with the CMA, adalimumab may be cost-saving compared with infliximab and with golimumab. However, this conclusion is dependent on the assumption of equal safety and efficacy for these biologics in the treatment of UC. The comparative cost-effectiveness of adalimumab compared with vedolizumab in patients with moderately to severely active UC is not known and could not be assessed by CDR. However, under an assumption of equal efficacy, safety, and usage, the use of adalimumab is likely cheaper than the use of vedolizumab, based on the available drug costs.

In jurisdictions where other biologic drugs are not available for use in UC, CDR suggests the ICUR for adalimumab + SOC compared with SOC alone may be between $67,000 per QALY and $130,000 per QALY. However, CDR notes that some areas of uncertainty were unable to be tested, which may impact the results.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table, and as such may not represent the actual costs to public drug plans.

TABLE 3: CADTH COMMON DRUG REVIEW COST COMPARISON TABLE FOR BIOLOGIC DRUGS FOR ULCERATIVE COLITIS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Adalimumab (Humira)[a]	40 mg/0.8 mL	Pre-filled syringe or auto-injector	740.36	160 mg at week 0, 80 mg at week 2, and 40 mg every 2 weeks thereafter	Year 1: 22,211 Thereafter: 19,249
Vedolizumab (Entyvio)	300 mg/vial	Powder for concentrate for solution for infusion	3,290.00 [b]	300 mg at weeks 0, 2, and 6, then every 8 weeks thereafter	Year 1: 26,320 Thereafter: 21,385
Golimumab (Simponi)[a]	50 mg/0.5 mL 100 mg/1.0 mL	Pre-filled syringe or auto-injector	1,520.21	200 mg at week 0, 100 mg at week 2, and 50 mg or 100 mg every 4 weeks thereafter	Year 1: 22,803 Thereafter: 19,763
Infliximab (Remicade)[c]	100 mg/10 mL	Vial for IV infusion	987.56	5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter[a]	Year 1: 31,602 Thereafter: 25,677

IV = intravenous; SEB = subsequent entry biologic; TNF = tumour necrosis factor; UC = ulcerative colitis.
[a] Assumes patient weight of 61 kg to 80 kg.
[b] Vedolizumab Common Drug Expert Committee (CDEC) recommendation.[11]
[c] Infliximab SEBs are not currently approved by Health Canada for use in UC, thus have not been included in Table 3.
Note: All prices are from the Ontario Drug Benefit Formulary and Exceptional Access Program (both accessed November 2015) unless otherwise indicated, and do not include dispensing fees; actual prices reimbursed by plans may be lower than those publicly listed or submitted to CDR.
Vedolizumab recently received a CDEC recommendation of "list with clinical criteria and conditions" for treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.[11]
Infliximab has Health Canada approval for this indication; however, the Canadian Expert Drug Advisory Committee (CEDAC) recommended infliximab not be listed for patients with moderately to severely active UC who have had an inadequate response to conventional therapy.[9] Despite this, infliximab is reimbursed by some Canadian provinces.
Golimumab has Health Canada approval for this indication; however, CDEC recommended golimumab not be listed at the submitted price for the treatment of UC.[10] It is not currently reimbursed by any jurisdiction for UC.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS ADALIMUMAB + SOC RELATIVE TO SOC FOR THE BASE CASE?

Adalimumab + SOC vs. SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$76,817 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS ADALIMUMAB + SOC RELATIVE TO SOC FOR THE WEEK 8 RESPONDER SUBGROUP?

Adalimumab + SOC vs. SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$65,154 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS ADALIMUMAB + SOC RELATIVE TO SOC FOR THE ANTI-TNF NAIVE SUBGROUP?

Adalimumab + SOC vs. SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$79,066 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SOC = standard of care; TNF = tumour necrosis factor; vs. = versus.

TABLE 7: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS ADALIMUMAB + SOC RELATIVE TO SOC FOR THE WEEK 8 RESPONDERS NAIVE TO ANTI-TNFS?

Adalimumab + SOC vs. SOC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$69,372 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; SOC = standard of care; TNF = tumour necrosis factor; vs. = versus.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 8: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?		X	
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	None		

TABLE 9: 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 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Adalimumab has been reviewed for ulcerative colitis (UC) by several health technology assessment (HTA) agencies, including the Pharmaceutical Benefits Advisory Committee (PBAC) (Australia), the Pharmaceutical Management Agency (PHARMAC) (New Zealand), the National Institute for Health and Care Excellence (NICE) (United Kingdom), the Haute Autorité de Santé (HAS) (France), and the Institut national d'excellence en santé et en services sociaux (INESSS) (Quebec). The relevant results available from HTA agencies are reported in the following paragraphs and in Table 10 and Table 11 below.

No economic analysis was submitted to HAS, and HAS found that adalimumab did not provide any improvement in actual benefit (IAB V) in the treatment of active, moderate to severe UC in patients who are intolerant to, or respond inadequately to, conventional treatments (corticosteroids, azathioprine, or 6-mercaptopurine). However, the HAS Transparency Committee recommended that adalimumab be included on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the new indication (UC).[37]

The INESSS committee recommended adalimumab not be listed, as its clinical benefit was judged to be insufficient.[38]

TABLE 10: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS (PBAC AND PHARMAC)

	PBAC (November 2013)[39]	PHARMAC (November 2013)[40]
Treatment	ADA (Humira) for the treatment of moderately to severe actively UC	
Price	Not reported	Not reported
Similarities With CDR Submission	The manufacturer submitted a Markov model, including 8 mutually exclusive health states that compared ADA (added to SOC) to SOC alone, using clinical data from ULTRA. Utility values were derived from Tsai et al.	
Differences With CDR Submission*	The model adopted a 20-year time horizon. The PBAC model stated three treatment status groups ("on assigned treatment", "on BSC only following discontinuation of assigned therapy", and "off medical treatment following surgery"). This does not appear to have been included in the submission to CDR.	
Manufacturer's Results	The manufacturer's economic evaluation produced an ICER in the range of $15,000 to $45,000 per QALY.	Not reported

	PBAC (November 2013)[39]	PHARMAC (November 2013)[40]
Issues Noted by the Review Group	PBAC noted that the structure of the economic model was not appropriate: • The proportions of patients on ADA, on BSC, and on no treatment were not correlated to the 8 health states in the model. • In subsequent cycles, patients with response/in remission were not treated with ADA or placebo. • The cost of ADA or BSC was not dependent on health states; health states accounted for only the cost of other health care resource use, while ADA costs were linked to ADA treatment. • The model did not include treatment discontinuations.	The committee considered the strength of the clinical evidence to be moderate overall, and weaker for long-term data. It also noted a high placebo effect in some trials. The committee noted that the efficacy of ADA and IFX were not directly compared, and that IFX is an appropriate comparator for CUA. The committee considered the increased risk of malignancy and infection, and the need for longer-term safety data.
Results of Reanalyses by the Review Group (If Any)	PBAC reported SA where costs of treatment were adapted to the health states. Partial Mayo scores, and alternative utility values were also used. ICURs ranged from A$45,000 to A$75,000 per QALY (input parameters), and from A$105,000 to A$200,000 per QALY (structural SA and multivariate analysis).	Not reported
Recommendation	PBAC rejected the submission on the grounds that the cost-effectiveness of ADA could not be appropriately estimated by the submitted economic analysis. PBAC also considered the requested listing to have a high and uncertain total cost for modest clinical benefit observed in trials.	The committee recommended that the application be declined because of limited evidence for sustained clinical effectiveness, lack of long-term safety data, and high financial risk.
Both PBAC and PHARMAC gave a negative recommendation for listing ADA for the treatment of UC. Both identified similar issues with the application, and although PBAC accepted BSC as an appropriate comparator, PHARMAC recently listed IFX, which they indicated should be the comparator.		

A$ = Australian dollar; ADA = adalimumab; BSC = best supportive care; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; IFX = infliximab; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); QALY = quality-adjusted life-year; SA = sensitivity analysis; SOC = standard care; TNF = tumour necrosis factor; UC = ulcerative colitis.
Note: Although not reported, it is likely that different prices were submitted to PBAC and PHARMAC than were submitted to CDR. Although it was not reported in the PBAC's Public Summary Document, adalimumab is listed at a price of $887.35 per unit on the Pharmaceutical Benefits Scheme. However, a risk-sharing arrangement may be in place.

Further to the November 2013 assessment of adalimumab submitted to PBAC, adalimumab was re-submitted to PBAC for consideration at its July 2014, July 2015, and November 2015 meetings.[41-45] At each meeting, PBAC rejected the application for listing. The submission for the July 2014 meeting presented a cost-utility analysis (CUA) of adalimumab compared with standard of care (SOC); however, as infliximab had been recommended at the March 2014 PBAC meeting, it was considered the most appropriate comparator. PBAC also noted that evidence presented for the comparison of adalimumab versus infliximab did not conclusively establish non-inferiority of adalimumab to infliximab.[43,44] The July 2015 and November 2015 recommendations were made on the basis that the evidence presented did

not establish non-inferiority of adalimumab versus infliximab (clarified in the November 2015 meeting minutes to indicate non-inferiority was not established in the maintenance phase), which invalidated the cost-minimization analyses (CMAs) presented by the manufacturer.[41,42,45]

TABLE 11: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS (NICE)

	NICE (February 2015)[46a]
Treatment	ADA SC injection, inducted as 160 mg at week 0 and 80 mg at week 2, maintenance dose of 40 mg EOW
Price	£352.14 per 40 mg pre-filled pen, syringe, or vial
Similarities to CDR Submission	• Comparative CE of ADA + CT vs. CT alone for patients with moderately to severely active UC with inadequate response to CT, with SA assessing patients who were TNF alpha naive • Ten-year TH and 2-week cycle length • Same model structure: 8 states (3 pre-surgery states, 1 surgery state, 4 post-surgery states) • Transition probabilities pre-surgery primarily derived from ULTRA 2 and ULTRA 3 • Transition probabilities for surgery and post-surgery based on published literature • Model included the following costs: drug, disease state, hospitalization, surgery, surgical complications, and surgery-related death • Costs derived from published literature
Differences to CDR Submission	• ULTRA 2 collected HRQoL data via SF-36, which was not transformed to SF-6D • Utility values were obtained from Swinburn[47] (pre-surgery) and Tsai[34] (post-surgery)
Manufacturer's Results	• Base-case ICER: £34,417/QALY gained • DSA ICER range: £29,437 to £38,073/QALY gained • PSA: at WTP of £30,000/QALY gained was 30% • Subgroup analysis for TNF alpha naive patients: ICER was £35,970/QALY gained
Issues Noted by the Review Group	AG critiqued company's decision problem, indicated it excluded other TNF alpha (GOL and IFX) and surgery as comparators, and deviated from project scope. AG also noted that mfr: • used a shorter cycle length than the time point for assessing induction in ULTRA 2 (6 weeks) • did not transform the data collected in ULTRA 2 using SF-36 to SF-6D utility values • assumed surgery improves utility score by 0.06 compared with active disease • modelled surgery rate based on questionable study. Based on above critiques and the general AG assessment, mfr undertook the following revisions: use lifetime TH, include general population mortality, derive ADA efficacy from TNF alpha naive subgroup from ULTRA trials, use mean surgery rate from 4 studies, and apply stopping rule to ADA. Revised ICER: £23,027 per QALY gained, not critiqued by AG.
Results of Reanalyses by the Review Group (If Any)	• AG developed de-novo model to assess comparative CE of ADA, GOL, and IFX (at licensed doses), and CT or surgery for moderate to severe UC post-tx failure. AG used lifetime TH divided into 2 phases; induction and maintenance; NHS perspective; cycle length for induction = 8 weeks, for maintenance = 26 weeks. • Model was probabilistic with 8 Markov states: 3 biologic tx (active disease, response, remission), 3 CT (same as biologic), post-surgery, death. Patients enter model at 40 years old, weighing 77 kg. If TNF alpha inhibitor led to response or remission in induction, patient continued same tx in maintenance phase; if not, patient stopped and switched to CT. Patients received TNF alpha maintenance as long as response/remission was maintained; if response was lost, patients received CT. Costs and QALYs were discounted at an annual rate of 3.5%. Patients on CT (from start or

	NICE (February 2015)[46a]
	later) continued CT in maintenance phase regardless of response, but could have surgery if disease remained active. Thus, surgery was included both as comparator (early) and intervention (later). All patients who had surgery remained in post-surgery until death. Various surgery rates and complication rates were used. • AG used Woehl et al. utilities in the base case and Swinburn et al. in SA. Dose escalation was based on clinical studies. IFX incurred administrative costs. • AGs base-case results indicated that surgery provides 14.72 QALYs at a cost of £41,921, which dominates ADA, GOL, IFX, and CT. ADA, GOL, and IFX had a 0% probability of being CE compared with surgery at WTP thresholds of £20,000 and £30,000 per QALY gained. • When data from Swinburn et al. were used, surgery was least effective but cheapest. GOL and CT were dominated. • ICER for ADA vs. surgery was £80,315 per QALY gained. ICER for IFX vs. ADA was £179,374 per QALY gained. • If surgery was not an option, IFX was dominated by ADA; GOL was extendedly dominated by ADA and CT. ICER for ADA vs. CT was £50,624 per QALY gained. • At a WTP threshold £20,000 per QALY gained, ADA had a 0% probability of being CE vs. CT, and a 5% probability of being CE at a WTP threshold of £30,000 per QALY gained. • The difference in effectiveness between biologics was small. • AG noted considerable uncertainty with extrapolation of short-term data to lifetime TH. Evidence of surgical complications was not identified in the systematic review.
Recommendation	ADA, GOL, and IFX could be recommended for treating moderately to severely active UC in adults with inadequate response to CT, or who cannot tolerate such therapy, or for whom such therapy is contraindicated.

ADA = adalimumab; AG = assessment group; CE = cost-effectiveness; CT = conventional therapy; DSA = deterministic sensitivity analysis; EOW = every other week; GOL = golimumab; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IFX = infliximab; mfr = manufacturer; NICE = National Institute for Health and Care Excellence (UK); PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SA = sensitivity analysis; TH = time horizon; TNF = tumour necrosis factor; tx = treatment; SC = subcutaneous; SF-36 = Short Form (36) Health Survey; SF-6D = Short Form (6-dimensional) Health Survey; UC = ulcerative colitis; WTP = willingness-to-pay.

[a] NICE recommendation pertained to three biologic treatments (infliximab, adalimumab, and golimumab) for treating moderately to severely active UC after the failure of conventional therapy. Table 11 attempts to focus on the manufacturer's model for adalimumab and AG critique.

APPENDIX 5: REVIEWER WORKSHEETS

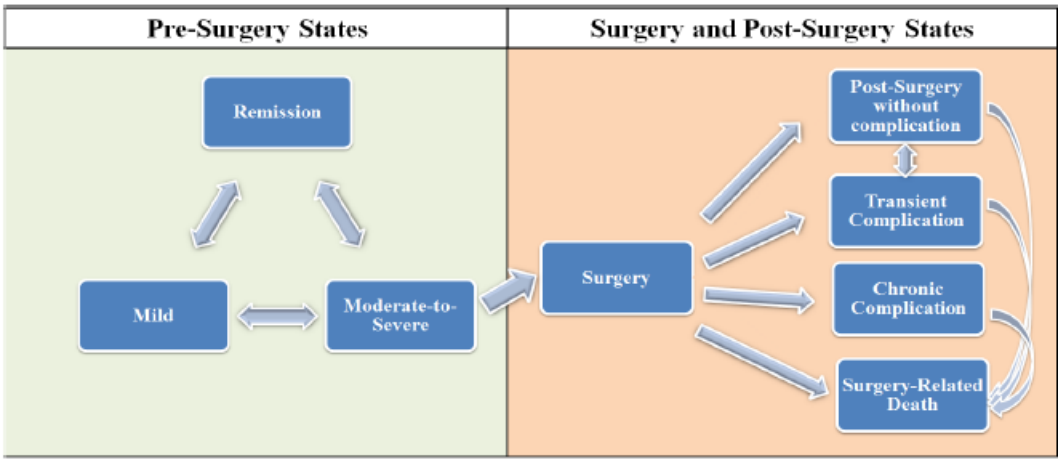
Manufacturer's model structure

The manufacturer submitted a cost-utility analysis (CUA) to estimate the incremental cost per quality-adjusted life-year (QALY) gained for the adalimumab and standard of care (SOC) combination therapy versus SOC treatment alone in patients with ulcerative colitis (UC), from the perspective of Canada's publicly funded drug plans.[1] The base-case model adopted a 10-year time horizon, with a two-week cycle length to accommodate the dosing schedule of alternative biologic treatments.

The manufacturer also undertook a de facto cost-minimization analysis (CMA) of adalimumab + SOC compared with golimumab + SOC and with infliximab + SOC, adding these regimens to the model but assuming equivalent efficacy, safety, and usage inputs for the golimumab and infliximab regimens as for adalimumab. The only difference assessed by the model was the incremental cost of treatment.

An eight-state Markov model was constructed to compare the cost-effectiveness of adalimumab + SOC versus SOC, generally categorized into pre-surgery, surgery, and post-surgery health states (Figure 1). At the beginning of each cycle, patients either remain in the health state or transition to a different health state based on a set of transitional probabilities. A half-cycle correction was applied to estimate costs and QALYs. The pre-surgery health states are based on disease severity: remission, mild, and moderate to severe. Patients transition between these states prior to surgery. These health states were defined using full Mayo scores from ULTRA 2 and ULTRA 3, or partial Mayo scores in the event that full Mayo scores were not available. The model assumed that a proportion of patients in the moderate to severe state would receive surgery; this was a tunnel state in the model, in which patients would stay for one cycle. Patients could not return to the surgery state. Four post-surgery health states were listed based on surgical outcome: post-surgery without complication, post-surgery with transient complication, post-surgery with chronic complication, and surgery-related death.

FIGURE 1: MODEL STRUCTURE



Source: Manufacturer's pharmacoeconomic submission.[1]

Transition matrices among the three pre-surgery health states were estimated between visits, where full Mayo score assessments were scheduled from visits in the ULTRA 2 trial and the ULTRA 3 extension trial, and from the published literature. Transition probabilities were estimated for adalimumab + SOC and

SOC alone for four specific time periods in the model: week 0 to week 8, week 8 to week 52, week 52 to week 104, and week 104 to week 520.

From week 0 to week 8, transition probabilities for patients in the moderate to severe state were based on ULTRA 2 trial data. However, transitions from the remission state or mild state could not be derived based on the trial data because all patients included in ULTRA 2 were moderate to severe; therefore, published literature was used for the estimation.[48,49] For patients who achieved remission between week 2 and week 8, it was assumed that the outcome for the SOC strategy would be the same as for non-adherent adalimumab patients using the 24-month rate and a constant hazard of loss of remission, while a similar process was used for the adalimumab + SOC group (using adalimumab-adherent patient data). The distribution among the remaining pre-surgery states (i.e., mild and moderate to severe) at week 8 was estimated in proportion to what was observed in the ULTRA 2 trial.

From week 8 to week 52, patient distributions among the three pre-surgery health states were generated based on ULTRA 2 trial data. Dose escalation was incorporated at this point for patients receiving adalimumab + SOC.

From week 52 to week 104, transition probabilities for SOC were assumed to be the same as those from week 8 to week 52, as generated from ULTRA 2; the extension study (ULTRA 3) did not assess SOC. For adalimumab + SOC, patient distributions among the three pre-surgery health states at week 0 (equivalent to week 52 of the ULTRA 2 trial) and week 48 of the ULTRA 3 extension trial were used to derive transitional probabilities. As patients with moderate to severe disease at week 8 were discontinued from adalimumab, only patients randomized to adalimumab and in remission or in the mild state at week 8 in ULTRA 2 were included. Dose escalation was incorporated at this point for patients receiving adalimumab + SOC.

From week 104 to week 520, similar to week 52 to week 104, the transitional probabilities for SOC were assumed to be the same as from week 8 to week 52. For adalimumab + SOC, as the ULTRA 3 extension trial is still ongoing, data from week 48 to week 240 were used to estimate the transitional probabilities of adalimumab patients from week 104 to week 520, using a multinomial logit regression model.

Subgroup analyses were undertaken on responders at week 8, patients naive to anti-TNF alpha drugs, and responders at week 8 who were naive to anti-TNF alpha drugs.

Although surgery data may have been available in the ULTRA trials, transitional probabilities in the surgery and post-surgery states were sourced from published literature containing real-world data. Surgery rates were estimated based on a weighted average of surgery rates from three publications that have specifically reported the rate of surgery among moderate to severe UC patients.[13-15] The post-surgery transient complication rate was sourced from a US-based publication[16] and the rate of post-surgery death was based on a UK study.[17] A constant hazard assumption was applied to estimate the transitional probabilities.

Utility values for all defined states in the model were not able to be sourced from a single source. The manufacturer indicated that Woehl et al. (2008),[33] Swinburn et al. (2012),[47] and Tsai et al. (2008)[34] fit best with the disease states. Woehl et al. (2008) and Swinburn et al. (2012) were identified as most useful for the pre-surgery states. As values from Woehl et al. were cited in the National Institute for Health and Care Excellence (NICE) technology appraisal[46] and other published literature, those values were used for the base case. Swinburn et al. was used for sensitivity analyses.[47] Utility associated with

surgery was not reported in the published literature, and as the manufacturer modelled surgery as a tunnel state, they assumed the utility value for surgery to be the same as that of moderate to severe UC. The manufacturer did not identify useful post-surgery chronic complication utility values. Chronic complications following surgery are varied, including chronic pouchitis, female infertility, and male sexual dysfunction. The manufacturer estimated a weighted value based on utilities from the published literature for these three complications,[50-52] and complication rates.[36,53-55]

Drug cost inputs for adalimumab, infliximab, and golimumab were obtained from the Ontario Drug Benefit Formulary.[18] An 8% markup fee was added to the drug costs of all biologics. The dosing schedules for each biologic treatment were based on product monographs.[19-21] Drug costs were based on an average body weight of 80 kg, and a 12.4% dose wastage rate was calculated assuming a normal distribution of the population weight.[22] Infusion costs for infliximab were not considered, as they are expected to be reimbursed by the manufacturer. SOC drug costs were obtained from an analysis of claims data from la Régie de l'assurance maladie du Québec (RAMQ) of 2,975 UC patients without Crohn disease from 2009 to 2011. Treatment compliance was based ULTRA 2 (year 1) and ULTRA 3 (subsequent years). Treatment compliance rates for other biologics were assumed to be the same as for adalimumab.

The medical costs for all pre-surgery states, the post-surgery without complication state, and the post-surgery with chronic complication state were estimated based on a survey of 40 Canadian gastroenterology physicians in 2013.[1] Moderate and severe health states were captured independently in the survey, but were combined and weighted based on physician feedback (64% moderate, 36% severe). Unit costs for examinations and specialist consultation visits were obtained from the Ontario Schedule of Benefits,[18] the Ontario Guide to Interdisciplinary Provider Compensation,[24] and the ONA collective bargaining agreement.[25] The surgery cost was incorporated as a one-time cost of an ileal pouch–anal anastomosis (IPAA) procedure (code S172) based on Ontario Ministry of Health and Long-Term Care.[23] Additional costs were considered for patients experiencing pouch failure. Hospitalization costs associated with surgery were sourced from the Ontario Case Costing Initiative.[26] Loftus et al. (2009)[56] reported that post-surgery complications included colectomy (2.8%), enterectomy (4.3%), and ostomy creation (8.7%). Medical costs for post-surgery transient complications were derived from Swenson et al.[16] No available literature reported end-of-life care cost associated with surgery-related death for UC patients, thus, the manufacturer assumed the cost of end-of-life care was equivalent to the cost of one hospital stay. Pre-surgery hospitalization rates were calculated using pooled data from ULTRA 1 and ULTRA 2 data (for a larger sample size). Infliximab and golimumab were assumed to have the same hospitalization rate as adalimumab. The unit cost associated with a hospital admission was obtained from the Ontario Case Costing Initiative.[26] All costs were inflated using the health care component of the Canadian Consumer Price Index and exchange-rate adjusted to 2014 Canadian dollars.

TABLE 12: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy: compared with SOC	Efficacy evidence for the ADA + SOC strategy and the SOC strategy in the pre-surgery disease states came from the primary pivotal study (ULTRA 2) and the OL extension trial (ULTRA 3).	Appropriate, although there is potential bias due to unblinding in ULTRA 2 trial, which might have been compromised due to injection site hypersensitivity. The earlier study (ULTRA 1) was excluded due to a different study design and significant protocol amendment.
Efficacy: compared with other biologics	The manufacturer noted that inherent differences in study design, setting, and end points evaluation between the trials of ADA, IFX, and GOL prevent a reliable IDC of these 3 biologics. The existing literature suggests potential comparable effectiveness of biologics in treating patients with moderately to severely active UC.[57,58] Therefore, the manufacturer assumed equivalence between ADA, GOL, and IFX.	VED was recently recommended for use by CDEC, but was not included by the manufacturer in its analysis. CDR identified five NMAs including ADA, GOL, IFX, PBO, and VED.[28-32] CDR Clinical reviewers found evidence from most IDCs supported superiority of the biologics over placebo in induction[28-32] and maintenance phases[28-30,32] for clinical response, clinical remission, and mucosal healing. However, small differences were observed between IDCs with regard to the NMA biologic comparisons. Several studies found IFX was statistically significantly favoured to ADA in the induction phase.[29,30,32] In only one NMA was a significant difference between the biologics identified for maintenance (favouring GOL over ADA).[30] However, there were substantial limitations with the conduct of the NMAs, leaving substantial uncertainty with regard to the comparative efficacy of ADA, GOL, IFX, and VED in maintenance treatment. Further information on the comparative clinical efficacy is provided in the CDR Clinical Report.
Natural history	Patients in the SOC alone arm of the ULTRA 2 trial were assumed to be representative of the natural history of patients with UC.	Likely to be appropriate.
Utilities	Utility values were not collected in either ULTRA 2 or ULTRA 3; thus were sourced from a review of the published literature.	NICE noted that the manufacturer collected SF-36 data in ULTRA 2, but did not transform the values to SF-6D utility values.[46]
Pre-surgery	Utility values for the pre-surgery states were sourced from Woehl et al.[33]	Study presented in abstract form only.

Data Input	Description of Data Source	Comment
Surgery	Utility associated with surgery was not reported in any study. Since surgery was modelled as a tunnel state, the authors assumed that the patient's health utility would remain unchanged.	Reasonable given the manufacturer's model structure and other assumptions.
Post-surgery	Post-surgery transient complication utility values were sourced from Tsai et al.[34] Chronic complication utility values were estimated based on compilation of utility values for chronic pouchitis, infertility, and male sexual dysfunction.[53-55] The values were weighted based on the rates of individual chronic complications. Disutility values for infertility and male sexual impotence were estimated by subtracting their respective disutility values of –0.18 and –0.07 from the utility for the state of post-surgery without complication.	The use of subtracting disutilities from a base value to determine a health state utility is not optimal, and is associated with high uncertainty. However, CDR notes there is a lack of data for the population that the manufacturer is interested in.
AEs	AEs were not considered in the model.	May favour the ADA + SOC strategy versus the SOC alone strategy.
Mortality	The model did not consider mortality other than surgery-related death. The rate of post-surgery death was based on a UK study.[17]	Based on the submitted time horizon, this assumption was deemed appropriate.
Resource use	The model considered the following components: administration, compliance, medical costs for each disease state, hospitalization, and end-of-life care.	
Drug	Dosing schedules for biologic treatments were based on product monographs.	Appropriate.
Compliance	Applied using ULTRA 2 and ULTRA 3 data. ULTRA 2 was applied for year 1. ULTRA 3 data were applied as the compliance rate after year 1.	As compliance rates were derived from a clinical study, compliance rates may be overestimated.
Event	Based on a resource utilization report of a survey of 40 Canadian gastroenterology physicians conducted by AbbVie.	
Health state	Based on a resource utilization report of a survey of 40 Canadian gastroenterology physicians conducted by AbbVie, and information from published literature.[56]	
Costs	Costs were reported in 2014 CAD.	
Drug	Drug cost inputs for ADA, GOL, and IFX were obtained from the Ontario Drug Benefit Formulary[18] and the MoHLTC. Drug cost of SOC was obtained from a claims analysis of the RAMQ database.	Biologic cost sources are appropriate. Use of RAMQ claims data may result in differences compared with other provinces in Canada, but these are unlikely to have a large impact on results.
Administration	Infusion costs were not included as they were expected to be reimbursed by the manufacturer.	Appropriate.

Data Input	Description of Data Source	Comment
Event: hospitalization	Procedure costs were sourced from Ontario MoHLTC and OCCI database.	Generally accepted as appropriate, although the limited access to the OCCI database hinders verification.
Health state	Based on published literature,[16] a Canadian physicians survey,[1] Ontario Schedule of Benefits,[18] Ontario Guide to Interdisciplinary Provider Compensation,[24] and ONA collective bargaining agreement.[25]	

ADA = adalimumab; AE = adverse event; CAD = Canadian dollars; CDEC = Canadian Drug Expert Committee; CDR = Common Drug Review; GOL = golimumab; IDC = indirect comparison; IFX = infliximab; MoHLTC = Ministry of Health and Long-Term Care; NICE = National Institute for Health and Care Excellence (UK); NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; ONA = Ontario Nurses Association; PBO = placebo; RAMQ = Régie de l'assurance maladie du Québec; SF-36 = Short Form (36) Health Survey; SF-6D = Short Form (six-dimensional) Health Survey; SOC = standard of care; UC = ulcerative colitis; VED = vedolizumab.

TABLE 13: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Patients on ADA who responded to induction therapy could have escalated dose if they relapsed to the moderate to severe state.	CDR clinical expert indicated this is appropriate.
Dose escalation was presented as a frequency dose escalation (from EOW to every week) based on data from ULTRA 2 ([redacted]% in Year 1) and ULTRA 3 ([redacted]%, and [redacted]% in Year 2 and subsequent years, respectively).	CDR clinical expert noted anecdotal evidence suggested dose escalation occurred in 15% to 17% of patients receiving ADA. However, an observational cohort study reported that 35% of ADA patients required dose escalation over the 13-month follow-up.[27] Thus, the model may have underestimated the costs associated with ADA dose escalation. Beyond Year 2, dose escalation is applied for the remainder of time the patients receives ADA (i.e., patient has mild/moderate disease).
Costs and disutilities associated with treatment-related SAEs were not considered in the model.	Not appropriate.
The placebo arm of the ULTRA 2 trial represented "SOC" in clinical practice.	May be appropriate.
Data from ULTRA 2 and ULTRA 3 were the primary sources used to populate the transition matrices.	While appropriate, the context of clinical trials data leads to some uncertainty in the transition probabilities. The extrapolation post-trial is particularly uncertain.
Patients who did not respond to the initial 8 weeks of biologic treatment discontinued and switched to SOC. Initial responders continued the biologic to week 104, dose escalating as required; no patients discontinued biologics in this period. From week 104 onwards, all patients who remained in the moderate to severe state discontinued biologics.	This does not appear to be a plausible assumption. The discontinuation rate in the one-year ULTRA 1 and ULTRA 2 were 27% and 38% in the adalimumab arms, and 30% and 47% in the placebo arm, respectively. The manufacturer assessed the impact of including discontinuation in a sensitivity analysis, which increased the ICUR.
Transition probabilities from remission or mild health states from week 2 to week 8 for SOC could not be derived from ULTRA 2;	Because of the model structure, it is not clear how reasonable this assumption is, and whether it may bias the model results.

Assumption	Comment
thus, were estimated from the literature. The probability of maintaining remission for SOC was the same as for non-adherent ADA patients (39%), and the probability of maintaining remission for ADA + SOC was the same as for adherent ADA patients (89%). A constant hazard of loss of remission was assumed to estimate the proportion of patients remaining in remission at week 8.	
Transition probabilities for SOC beyond week 52 were assumed to be the same as those of week 8 to week 52.	Likely to be appropriate.
The proportions of patients who had moderate disease compared to severe disease for health states were derived from physician estimates that 20.7% of patients were moderately ill and 11.8% were severely ill. Thus, the proportion of moderately ill and severely ill (64% and 36%, respectively) was used to weight values where required.	CDR clinical expert indicated this assumption was reasonable.
A constant hazard assumption was applied to estimate the 2-week transition probabilities for all post-surgery health states.	CDR clinical expert indicated that the assumption of a risk post-surgery is unlikely to be appropriate. The risks of transient complications post-surgery or surgical failure would be higher during the first 12 months after surgery, and decrease as time went on.
Surgery was modelled as a tunnel state; therefore the utility value would remain unchanged from its previous value (moderate to severe state). Patients are in the surgery health state for one cycle.	Reasonable given the manufacturer's model structure and other assumptions.
Only patients with moderate to severe disease would receive surgery.	Generally accepted as appropriate, although the CDR clinical expert noted that some patients with mild disease who also have malignancy would require surgery. (This would not be due to level of disease, but rather to other complications.)
The rate of surgery failure used was determined based on rates from a US paper,[56] using estimates from three surgical failure responses (colectomy, enterectomy, and ostomy creation). The rates were assumed to be constant over time.	The manufacturer assumed that the total rate of surgery failure was approximately 16% per annum in total. Although these figures appear appropriate for the study setting (mid-2000s US), it is possible that practice differs in Canada and that surgical outcomes may have improved in recent years. A higher surgery rate favours adalimumab, although the effect on the ICUR is not large. (See earlier notes on the use of a constant surgery rate.)
All long-term complications occur in the first cycle after surgery, and all patients remain in that state for the remainder of the model.	The CDR clinical expert indicated that this is unlikely to be the case. This is likely to favour the ADA + SOC strategy versus the SOC alone strategy.
Mortality following surgery was modelled, but due to the short time horizon, death was not modelled during the pre-surgery	Given the average age of patients with UC (~40 years),[59-62] and the duration of the model (10 years), it may have been appropriate to include general population mortality rates.

Assumption	Comment
stages.	
Surgery-related death would occur in the hospital; thus, the cost of end-of-life care is equivalent to the cost of one hospitalization.	This is likely to be appropriate.
Surgical outcomes are not impacted by patient's pre-surgery treatment.	The CDR clinical expert noted that, in theory, ADA may be associated with decreased immune response, which might lead to increased rates of infection post-surgery; however, the clinical expert had yet to see this in practice and noted this would likely be the same for all biologics.
Patients could enter the post-surgery transient complication state at any cycle after surgery.	Appropriate.
The rate of hospitalization was based on data from ULTRA 1 and ULTRA 2.[12,59]	CDR identified uncertainty surrounding the use of data from ULTRA 1 given the study design and protocol change. However, altering the hospitalization rate does not appear to have a substantial impact on the model results.
The efficacy for IFX + SOC and GOL + SOC was assumed to be the same as for ADA + SOC.	CDR clinical expert indicated that this is generally accepted.
Dose escalation rates for other biologics were assumed to be the same as for ADA.	CDR clinical expert indicated this assumption may not be appropriate, and that the dose escalation of ADA in Crohn disease is generally 15% to 17%, while for IFX, it is nearly double (30%). CDR notes any assumptions regarding a change in dosing for IFX will also impact potential wastage.
Compliance rates for other biologics were assumed the same as for ADA.	CDR clinical expert noted that it is easier to track compliance with IFX as physicians are informed if patients do not show up, whereas it is more difficult to track compliance in patients receiving non-infusion treatments.
Hospitalization rates for other biologics were assumed to be the same as for ADA.	Considered appropriate.
An average body weight of 80 kg was assumed for IFX based on the ACT-1 trial,[22] with a 12.4% dose wastage rate included (assuming a normal distribution of the population weight).[22]	IFX is available as a single-use vial, with patients weighing 61 to 80 kg requiring 4 vials, and patients weighing 81 kg to 100 kg requiring 5 vials. The average weight in ULTRA 2 and ACT-1 were below 80 kg. CDR tested the results without wastage for IFX.
Inclusion of an 8% markup for the biologics.	Not considered appropriate. The 8% markup was removed in CDR reanalyses.

ADA = adalimumab; CDR = CADTH Common Drug Review; EOW = every other week; GOL = golimumab; ICUR = incremental cost-utility ratio; IFX = infliximab; SAE = serious adverse event; SOC = standard of care; UC = ulcerative colitis; VED = vedolizumab.

Validation

The manufacturer stated that the estimates of pre-surgery transitional probabilities were validated by comparing the model output on patient disposition to the observed patient distribution at available time points in the ULTRA 2 and ULTRA 3 trials. For adalimumab + SOC and SOC alone, the differences between predicted and observed percentages were all smaller than 0.5 per cent points at week 8 and week 52. For adalimumab + SOC at week 100, the model performed equally well when estimating patients in the mild state, but it slightly underestimated patients in the remission state and slightly

overestimated patients in the moderate to severe state. By week 292, the discrepancy between the predicted and observed patients in the remission and mild states became larger (9.1% points). This is likely due to the smaller sample size by week 292; thus, the prediction was less stable.

Manufacturer's sensitivity analyses

The manufacturer undertook one-way sensitivity analyses on both the CUA and CMA, testing parameters and assumptions related to treatment costs, medical costs, indirect costs, utilities, transitional probabilities, annual discount rate, and time horizon.

The manufacturer also undertook a probabilistic sensitivity analysis (PSA), testing medical costs, utilities, and transition probabilities. The PSA used beta distributions for the utilities and transitional probabilities, and gamma distributions for cost parameters. A Monte Carlo simulation of 1,000 random draws from all parameters of uncertainty was undertaken, and the incremental cost and effectiveness was estimated for each simulation. Results were reported using scatterplots (CUA) and histograms (CMA), and a cost-effectiveness acceptability curve (CEAC) was generated to illustrate the percentage of simulations that had a value falling below different WTP thresholds.

Manufacturer's subgroup analyses

The manufacturer undertook three subgroup analyses, assessing the cost-effectiveness of adalimumab + SOC versus SOC alone in the following populations:

- responders to adalimumab induction therapy who were anti-TNF alpha naive or anti-TNF alpha experienced
- patients who were anti-TNF alpha naive
- responders to adalimumab induction therapy who were anti-TNF alpha naive.

Manufacturer's results

The manufacturer's base-case analysis reported that over a 10-year period, adalimumab + SOC was associated with an ICUR of approximately $77,000 per QALY compared with SOC alone (Table 14).

TABLE 14: SUMMARY OF RESULTS OF THE MANUFACTURER'S COST-UTILITY ANALYSIS BASE CASE

	ADA + SOC	SOC	Incremental
Pre-surgery costs	$98,042	$32,858	$65,184
Surgery and post-surgery costs	$22,885	$31,428	–$8,543
Total costs	$120,927	$64,286	$56,642
Total QALYs	4.7635	4.0262	0.7374
ICUR			**$76,817**

ADA = adalimumab; CUA = cost-utility ratio; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.
Note: Only discounted values are presented.
Source: Adapted from manufacturer's pharmacoeconomic submission.[1]

The manufacturer's base-case analysis included an 8% markup fee for the biologic treatments. When this markup was removed, the base-case incremental cost-utility ratio (ICUR) was reduced to $69,819 per QALY.

The manufacturer's CMA comparing adalimumab + SOC with golimumab + SOC and with infliximab + SOC considered only the biologics cost, as the biologics were assumed to have the same efficacy and

safety. Other medical and drug costs were assumed to be equal between biologics treatments. The results for a 10-year time horizon indicate that adalimumab is cost-saving compared with golimumab and with infliximab (Table 15).

TABLE 15: SUMMARY OF RESULTS OF THE MANUFACTURER'S COST-MINIMIZATION ANALYSIS BASE CASE

	ADA + SOC	GOL + SOC	IFX + SOC	ADA + SOC vs. GOL + SOC	ADA + SOC vs. IFX + SOC
Cost of biologic	$69,658	$75,537	$105,327	–$5,878	–$35,669
Other medical and drug costs	$51,269	$51,269	$51,269	$0	$0
Total costs	$120,927	$126,806	$156,596	–$5,878	–$35,669

ADA = adalimumab; CMA = cost-minimization analysis; GOL = golimumab; IFX = infliximab; SOC = standard of care; vs. = versus.
Note: Only discounted values are presented.
Source: Adapted from the manufacturer's pharmacoeconomic submission.[1]

When the 8% markup fee was removed, the results did not change markedly.

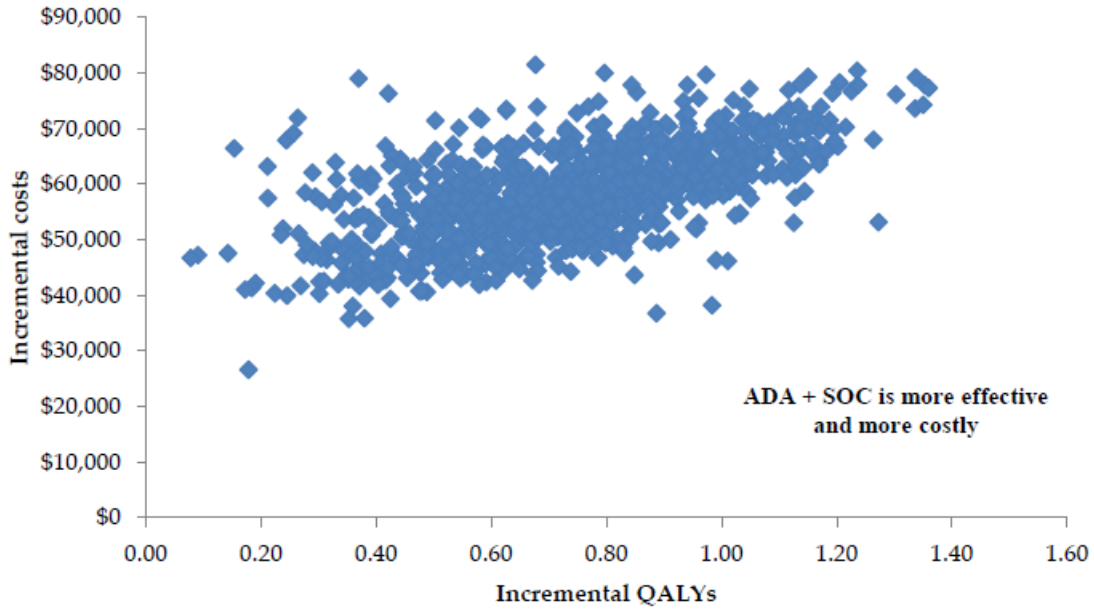
Manufacturer's sensitivity analysis results

The manufacturer undertook one-way sensitivity analyses on the CUA to test parameters and assumptions related to treatment costs, medical costs, indirect costs, utilities, transitional probabilities, and annual discount rate. The results indicated the model was reasonably stable, reporting ICURs ranging from approximately $53,000 (including indirect costs) to approximately $94,000 (five-year time horizon) per QALY gained.

One-way sensitivity analyses were undertaken on the CMA as well, testing small adjustments in treatment costs (± 5%), dose and discontinuation rates, transitional probabilities, and time horizon. Adalimumab + SOC was cost-saving compared with the other biologics in all parameters tested.

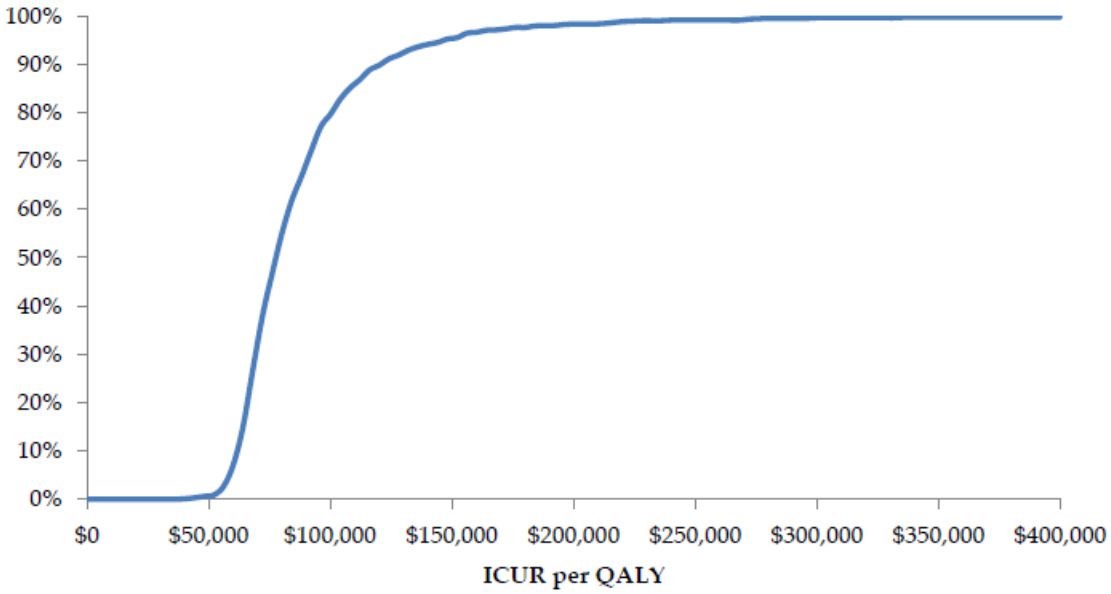
The results of the PSA indicated a mean (95% confidence interval) ICUR per QALY of $87,427 ($84,979 to $89,874), a median ICUR per QALY of $77,434, and a standard deviation of $39,488 (per scatterplot). The CEAC indicates that in 80% of simulations, the ICUR was below a WTP threshold of $100,000 per QALY gained; and at a $125,000 per QALY gained WTP threshold, 91% of simulations found adalimumab + SOC to be cost-effective (CEAC). At a WTP threshold of $50,000 per QALY gained, there is a near 0% probability that adalimumab + SOC is cost-effective compared with SOC alone.

FIGURE 2: PROBABILISTIC SENSITIVITY ANALYSIS SCATTERPLOT RESULTS



ADA = adalimumab; QALY = quality-adjusted life-year; SOC = standard of care.
Source: Manufacturer's pharmacoeconomic submission.[1]

FIGURE 3: PROBABILISTIC SENSITIVITY ANALYSIS COST-EFFECTIVENESS ACCEPTABILITY CURVE RESULTS



ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[1]

The results of the PSA on the CMA indicated that adalimumab + SOC was less costly in all simulations when compared with infliximab + SOC (a mean incremental cost of –$35,948, a median of –$35,968, and a standard deviation of $4,603) and with golimumab + SOC (a mean incremental cost of –$5,893, a median of –$5,892, and a standard deviation of $247).

Manufacturer's subgroup analysis results: week-8 responders, adalimumab + SOC versus SOC
In the subgroup of patients who responded to adalimumab induction therapy at week 8, the manufacturer reported that over the 10-year time horizon, adalimumab + SOC was associated with incremental costs of $108,602 and incremental QALYs of 1.6669, resulting in an ICUR of $65,154 per QALY gained.

Manufacturer's subgroup analysis results: patients naive to biologics, adalimumab + SOC versus SOC
In the subgroup of patients who were naive to biologics, the manufacturer reported that over the 10-year time horizon, adalimumab + SOC was associated with incremental costs of $68,769 and incremental QALYs of 0.8698, resulting in an ICUR of $79,066 per QALY gained.

Manufacturer's subgroup analysis results: week-8 responders and naive to biologics, adalimumab + SOC versus SOC
In the subgroup of patients who responded to adalimumab induction therapy at week 8 and were naive to biologics, the manufacturer reported that over the 10-year time horizon, adalimumab + SOC was associated with incremental costs of $109,880 and incremental QALYs of 1.5839, resulting in an ICUR of $69,372 per QALY gained.

CADTH Common Drug Review reanalyses

The manufacturer undertook its analysis assuming an 8% markup on all biologics in the model. CADTH Common Drug Review (CDR) removed this markup when undertaking all reanalyses. CDR reanalyses assessed the cost-effectiveness of adalimumab + SOC compared with SOC alone, excluding the 8% markup.

For ADA + SOC versus SOC alone
There is substantial uncertainty with the utility estimates: The manufacturer identified a large number of utility values, which indicated a wide variability, leading to uncertainty in the values used.[33,34,47,51,63-65] The post-surgery states in the model were primarily based on utility estimates reported by Tsai et al.[34] While Tsai et al. indicate in their article that the utility values are sourced from a survey of UK patients using the EuroQol 5-Dimensions Questionnaire (EQ-5D), the reference that is presented — as an abstract only — for the utility values does not appear to include the reported utility values, unless they are based on incidence, admission, and re-admission rates.[35] The pre-surgery utility values were based on data presented in an abstract by Woehl et al.[33] There is some uncertainty with the information provided in Woehl et al., given the lack of information provided on the study. CDR also notes that the external validity of the association between the different health state utility values used in the manufacturer's base case was not demonstrated by the manufacturer.

The manufacturer tested some utility values in sensitivity analyses on its base case; each of these one-way sensitivity analyses indicated an ICUR higher than the base case. CDR undertook a sensitivity analysis using values higher and lower than the manufacturer's base case to test the volatility with the values used (Table 16).

TABLE 16: SUMMARY OF CADTH COMMON DRUG REVIEW UTILITY VALUES FOR THE REANALYSES

Health State	Manufacturer Utility Values Used	Range Used by CDR [a]	
		Lower Values	Upper Values
Remission	0.87	0.79	0.91[b]
Mild UC	0.76	0.76	0.80
Moderate to severe UC	0.41	0.32	0.66
Surgery	0.41	0.32	0.66
Surgery with no complications	0.61	0.60	0.66[a]
Surgery with transient complications	0.55	0.42	0.55
Surgery with chronic complications	0.43	0.40	
Death related to surgery	0.00	0.00	

CDR = CADTH Common Drug Review; UC = ulcerative colitis.
[a] The upper value was reported in the literature to be 0.61; however, it is counterintuitive that coming through surgery without complications will lead to a health state utility value lower than that used in the actual surgery health state.
[b] The paper by Poole et al. (2010)[64] presented a higher utility value for the remission state (0.94), but published data[66] indicate that this value is higher than the mean utility of the general population in Canada; hence, the second highest available value for this health state was used as appropriate, in this context, from Swinburn et al. (2012).[47]

The surgery rate may be overestimated: The manufacturer indicated that the probability of transitioning to the surgery health state equated to approximately 11% per year (0.0044 every two weeks), based on data pooled from three publications that reported the rate of surgery in patients with moderate to severe UC, and steroid-refractory severe UC.[13-15] However, CDR notes that Targownik et al.[36] reported the rate of colectomy was 3.6% at one year, 7.6% at five years, and 10.4% at 10 years. The CDR clinical expert indicated that the rate of surgery has decreased in recent years, indicating that the rate of surgery is likely to be somewhere between the 11% per year in the model and 5% per year. CDR thus tested a lower surgery rate in the model (0.0020 every two weeks).

Rate of dose escalation may be underestimated: The manufacturer considered rates of dose escalation for adalimumab as per the ULTRA trials ([redacted]%, [redacted]%, and [redacted]% in year 1, year 2, and thereafter, respectively). However, these rates might not reflect the dose escalation rates seen in Canadian practice. Additionally, the CDR clinical expert reported that dose escalation can be offered by increasing dose strength (40 mg to 80 mg), or by increasing both the dose frequency and strength. Furthermore, an observational cohort study of UC patients indicated that 35% of patients treated with adalimumab required dose escalation over 13 months.[27] Therefore, the model might have underestimated the costs associated with dose escalation of adalimumab. The CDR clinical expert did note that the rate of dose escalation for adalimumab in Crohn disease ranged from 15% to 17% per year (anecdotal evidence). Thus, CDR undertook reanalyses for two scenarios, the first assuming a constant 15% rate of dose escalation, and the second assuming a dose escalation rate of 30% in year 1, then returning to the values from ULTRA 3 in subsequent years.

SOC costs may be underestimated: The manufacturer assumed a cost per two-week cycle of approximately $27 for SOC based on data from Rutgeerts et al.[22] Data from ULTRA 2 indicated that approximately 93% of patients received some form of standard UC treatment at study baseline: 65% received corticosteroids (such as prednisone), 38% received either 6-mercaptopurine or azathioprine, and 66% received an aminosalicylate (such as mesalazine). Thus, CDR undertook an analysis revising the cost of SOC based on standard treatment costs and regimens for the aforementioned drugs. The cost per cycle for SOC was calculated to be approximately $58.

Treatment discontinuation between week 8 and week 104 was not considered: The manufacturer's base case assumed that no patients would discontinue treatment between week 8 (the end of the induction period) and week 104. However, the discontinuation rate in ULTRA 1 and ULTRA 2 studies were 27% and 38% in the adalimumab arm, respectively, and 30% and 47% in the placebo arm, respectively. The CDR clinical expert indicated that it was expected that patients would discontinue or take a drug holiday at some point between week 8 and week 104; thus, CDR undertook reanalyses including treatment discontinuation between week 8 and week 104. The manufacturer included a discontinuation rate in its sensitivity analyses; thus, CDR used this analysis in its reanalysis.

TABLE 17: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSES FOR ADALIMUMAB + SOC VERSUS SOC ALONE

Analysis	ADA + SOC QALYs	SOC Alone QALYs	QALY Difference (ADA+SOC vs. SOC Alone)	ADA + SOC Costs	SOC Alone Costs	Cost Difference (ADA+SOC vs. SOC Alone)	ICUR (ADA+SOC vs. SOC Alone)
Manufacturer's base case	4.7635	4.0262	0.7374	$120,927	$64,286	$56,642	$76,817
Manufacturer's base case, excluding 8% markup	4.7635	4.0262	0.7374	$115,767	$64,286	$51,482	$69,819
CDR One-way Reanalyses							
1. Utility values (lower values)	4.2821	3.5586	0.7235	$115,767	$64,286	$51,482	$71,157
2. Utility values (upper values)	5.7194	5.2237	0.4957	$115,767	$64,286	$51,482	$103,857
3. Surgery rate per cycle = 0.0020	4.7198	3.9470	0.7728	$111,675	$57,482	$54,193	$70,123
4. Dose escalation (lower values)	4.7635	4.0262	0.7374	$114,013	$64,286	$54,747	$67,440
5. Dose escalation (upper values)	4.7635	4.0262	0.7374	$117,810	$64,286	$53,524	$72,590
6. Cost of SOC increased	4.7635	4.0262	0.7374	$120,648	$68,624	$52,024	$70,555
7. Include treatment discontinuation[a]	NA	NA	0.5664	NA	NA	$42,300	$74,678
CDR Multi-way Reanalyses							
8. Multi-way analyses (1, 3, 4)	4.1799	3.3989	0.7809	$109,877	$57,482	$52,395	$67,093
9. Multi-way analyses (1, 3, 4, 7)	NA	NA	0.5917	NA	NA	$42,624	$72,037
10. Multi-way analyses (2, 3, 5, 6)	5.8302	5.3640	0.4662	$119,308	$62,769	$56,539	$121,282
11. Multi-way analyses (2, 3, 5, 6, 7)	NA	NA	0.3535	NA	NA	$46,041	$130,253

ADA = adalimumab; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; NA = not available; SOC = standard of care; vs. = versus.

[a] As reported from the manufacturer's deterministic sensitivity analysis.

For ADA + SOC compared with biologics + SOC

There is uncertainty surrounding the potential wastage associated with infliximab: The manufacturer assumed dose wastage for infliximab based on data from Rutgeerts et al.[22] The data suggest the average weight for a patient receiving infliximab was 80 kg, based on Rutgeerts et al. (ACT-1 trial).[22] The manufacturer calculated a dose wastage rate of 12.4%, assuming of a normal distribution on the standard deviation (17.8 kg). These values are supported by data from ACT-2.[22] The CDR clinical expert indicated that wastage was generally kept to a minimum, as the dose of infliximab could be managed to reduce wastage, rounding to the nearest full vial as required. The CDR clinical expert noted that infliximab may be dosed up to 10 mg/kg to avoid wastage. CDR undertook reanalyses, varying the level of wastage from 0% to 20%. In both circumstances, adalimumab was less costly than both infliximab and golimumab at the current prices.

Rate of dose escalation may be underestimated: The manufacturer considered rates of dose escalation, as seen in ULTRA trials ([redacted]%, [redacted]%, and [redacted]% in year 1, year 2, and thereafter, respectively), would be applicable not only to adalimumab, but also to infliximab and golimumab. The CDR clinical expert indicated that the rate of dose escalation for adalimumab in Crohn disease in clinical practice ranges from 15% to 17% per year (anecdotal evidence), approximately half that seen with infliximab (30%; anecdotal). However, an observational cohort study of UC patients indicated that 35% of patients treated with adalimumab required dose escalation over 13 months.[27] Therefore, CDR undertook reanalyses for two scenarios:

1. Adalimumab: constant 15% rate of dose escalation
   Infliximab: constant 30% rate of dose escalation
   Golimumab: remains as per the ULTRA trials
2. Adalimumab: dose escalation rate of 30% in year 1, then returning to the values from ULTRA 3 in year 2 and subsequent years (as per the manufacturer's assumptions)
   Infliximab: constant 30% rate of dose escalation
   Golimumab: remains as per the ULTRA trials

Cost savings assumed for adalimumab versus infliximab are based on assumptions of patient weight: Patients who weigh 60 kg or less would require fewer vials of infliximab; thus, adalimumab may have an incremental cost compared with infliximab in these patients. For patients weighing 100 kg, adalimumab may have increased cost savings compared with infliximab. CDR undertook two reanalyses based on patient weight. In these analyses, CDR assumed no dose wastage. In both circumstances, adalimumab was less costly than both infliximab and golimumab at the current prices.

TABLE 18: SUMMARY OF CADTH COMMON DRUG REVIEW REANALYSES FOR ADALIMUMAB + SOC VERSUS BIOLOGIC + SOC

Analysis	Cost of ADA ($)	Cost of GOL ($)	Cost of IFX ($)	Incremental cost (ADA to GOL) ($)	Incremental cost (ADA to IFX) ($)
Manufacturer's base case	120,927	126,806	156,596	–5,878	–35,669
Manufacturer's base case	115,767	121,210	148,794	–5,443	–33,026
CDR reanalyses					
Decrease IFX wastage to 0%	115,767	121,210	138,027	–5,443	–22,260
Increase IFX wastage to 20%	115,767	121,210	155,379	–5,443	–39,612
Dose escalation scenario 1	114,013	121,210	156,719	–7,198	–42,706
Dose escalation scenario 2	117,810	121,210	156,719	–3,400	–38,909
Patients weighing 60 kg	115,767	121,210	116,338	–5,443	–570
Patients weighing 100 kg	115,767	121,210	159,717	–5,443	–43,950

ADA = adalimumab; CDR = CADTH Common Drug Review; GOL = golimumab; IFX = infliximab; SOC = standard of care.

APPENDIX 6: COST TABLE FOR OTHER NON-BIOLOGIC TREATMENTS FOR ULCERATIVE COLITIS

TABLE 19: COST TABLE FOR NON-BIOLOGIC TREATMENTS FOR ULCERATIVE COLITIS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Average Daily Drug Cost ($)	Average Annual Cost ($)
Aminosalicylates						
5-ASA (Asacol, Asacol 800)	400 mg	Tab	0.3951	Active: 0.8 g to 3 g daily in divided doses Maintenance: 1.6 g daily in divided doses	0.79 to 4.74 1.58	288 to 1,731 577
	800 mg	Ent. tab	1.0938	4.8 g daily in divided doses	6.56	2,395
5-ASA (Novo-5-ASA)	400 mg	Tab	0.3951	Active mild/moderate: 2 tabs to 8 tabs in divided doses (max/severe: 12 tabs daily) Maintenance: 4 tabs in divided doses	0.79 to 4.74 1.58	288 to 1,731 577
5-ASA (Mesasal)	500 mg	Ent. tab	0.6368	Active: 1.5 g to 3 g tabs daily in divided doses Maintenance: 1.5 g daily in divided doses	1.91 to 3.82 1.91	697 to 1,395 697
5-ASA (Mezavant)	1.2 g	Delayed and extended-release tab	1.6253	Induction: 2 tabs to 4 tabs once daily Maintenance: 2 tabs once daily	3.25 to 6.50 3.25	1,186 to 2,373 1,186
5-ASA (Pentasa)	500 mg 1,000 mg	Delayed-release tab	0.5569 1.1138	2 g to 4 g daily in divided doses	2.23 to 4.46	813 to 1,626
	1 g 1 g/100 mL 4 g/100 mL	Supp Enema Enema	1.6000 3.7000 4.4600	Supp: 1 g daily Enema: 1 g to 4 g daily	1.60 3.70 to 4.46	584 1,350 to 1,628
5-ASA (Salofalk)	500 mg	Ent. tab	0.5817	3 g to 4 g daily in divided doses	3.49 to 4.65	1,274 to 1,699
	500 mg 1,000 mg	Supp Supp	1.2855 1.8887	Supp: 1 g to 1.5 g daily	1.89 to 3.86	689 to 1,408
	2 g/60 g 4 g/60 g	Rect Susp	4.1500[a] 7.0351	Active: 4 g nightly Maintenance: 2 g nightly or 4 g every	7.04	2,568

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Average Daily Drug Cost ($)	Average Annual Cost ($)
				two nights	3.52 to 4.15	1,287 to 1,515
Olsalazine (Dipentum)	250 mg	Capsule	0.5330	Active: 1 g to 3 g daily in divided doses Maintenance: 1 g daily in divided doses	2.13 to 6.40 2.13	778 to 2,335 748
Sulfasalazine (Salazopyrin) 	500 mg 500 mg	Tab Ent. tab	0.2593 0.3950	Active: 1 g to 2 g three to four times daily Maintenance: 1 g two to three times daily	1.56 to 6.32 1.04 to 2.37	568 to 2,307 379 to 865
Sulfasalazine (generic) 	500 mg 500 mg	Tablet Ent. tab	0.1804 0.2816	Active: 1 g to 2 g three to four times daily Maintenance: 1 g two to three times daily	1.08 to 4.51 0.72 to 1.69	395 to 1,645 263 to 617
Immunosuppressants						
6-mercaptopurine (Purinethol and generic)	50 mg	Tab	2.8610	50 mg to 100 mg daily	2.86 to 5.72	1,044 to 2,088
Azathioprine (Imuran)	50 mg	Tab	1.0369	2.5 mg/kg daily	4.15[b]	1,514
Azathioprine (generic)	50 mg	Tab	0.2405	2.5 mg/kg daily	0.96[b]	351
Corticosteroids, Topical						
Betamethasone disodium phosphate (Betnesol)	5 mg/ 100 mL	Enema	10.3486	5 mg nightly	10.35	3,777
Budesonide (Entocort)	0.02 mg/mL	Enema (100 mL)	8.5200[a]	2 mg nightly	8.52	3,110
Hydrocortisone (Cortenema) (Cortifoam)	100 mg/ 60 mL 15 g/pack (14 doses)	Enema Rect. Aerosol	7.2711 90.7000	60 mL nightly or every other night One dose nightly or every other night	3.64 to 7.27 3.24 to 6.48	1,327 to 2,654 1,182 to 2,365

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Average Daily Drug Cost ($)	Average Annual Cost ($)
Corticosteroids, Systemic						
Hydrocortisone (Solu-Cortef)	100 mg 250 mg	Vial	3.7200[a] 6.4500[a]	300 mg to 400 mg IV daily	10.17 to 12.90	NA
Prednisone (generics)	1 mg 5 mg 50 mg	Tab	0.1066 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

5-ASA = 5-aminosalicylic acid (mesalamine/mesalazine); ent = enteric coated; IV = intravenous; NA = not available; rect = rectal; sup = suppository; tab = tablet.
[a] Saskatchewan Formulary (November 2015).
[b] Assumes 80 kg patient weight.
Note: All prices are from the Ontario Drug Benefit Formulary (November 2015) unless otherwise indicated.

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission: Humira (adalimumab) for ulcerative colitis, 40 mg in 0.8 mL sterile solution (50 mg/mL). Company: AbbVie Corporation. [**CONFIDENTIAL** manufacturer's submission]. Dorval (QC): AbbVie Corporation; 2015 Oct 27.
2. Common Drug Review. CEDAC final recommendation and reasons for recommendation. Adalimumab (Humira™ - Abbott Laboratories, Limited) [Internet]. Ottawa: CCOHTA; 2005. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira%28adalimumab%29Feb11-05.pdf
3. Common Drug Review. CEDAC final recommendation and reasons for recommendation. Adalimumab resubmission (Humira® - Abbott Laboratories Ltd.) [Internet]. Ottawa: CADTH; 2006. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira_Resubmission_Nov29-06.pdf
4. Common Drug Review. CEDAC final recommendation on reconsideration and reasons for recommendation. Adalimumab resubmission #2 (Humira® for ankylosing spondylitis - Abbott Laboratories Ltd.) [Internet]. Ottawa: CADTH; 2007. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira_Resubmission_June-27-2007.pdf
5. Common Drug Review. CEDAC final recommendation and reasons for recommendation. Adalimumab resubmission #3 (Humira® - Abbott Laboratories Ltd.) [Internet]. Ottawa: CADTH; 2007. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira-Resubmission-Crohns_Dec-19-2007.pdf
6. Common Drug Review. CEDAC final recommendation and reasons for recommendation. Adalimumab (Humira® - Abbott Laboratories Ltd.). New indication: psoriasis [Internet]. Ottawa: CADTH; 2008. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira-Psoriasis_October_2008.pdf
7. Common Drug Review. CADTH Canadian Drug Expert Committee final recommendation. Adalimumab (Humira - AbbVie Corporation). New indication: polyarticular juvenile idiopathic arthritis [Internet]. Ottawa: CADTH; 2013. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Humira-JIA_July-22-13_e.pdf
8. Adalimumab [Internet]. Ottawa: CADTH; 2013 Dec 23. [cited 2016 Jan 12]. (Submission status report). Available from: https://www.cadth.ca/adalimumab-50
9. Common Drug Review. CEDAC final recommendation and reasons for recommendation. Infliximab (Remicade® - Centocor Inc.). Indication: ulcerative colitis [Internet]. Ottawa: CADTH; 2009. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_Remicade_Final_April_24_2009.pdf
10. Common Drug Review. CADTH Canadian Drug Expert Committee final recommendation. Golimumab (Simponi - Janssen Inc.). New indication: ulcerative colitis [Internet]. Ottawa: CADTH; 2014. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0341_complete_Simponi_Mar-28-14.pdf

11. Common Drug Review. CADTH Canadian Drug Expert Committee final recommendation. Vedolizumab (Entyvio - Takeda Canada Inc.). Indication: ulcerative colitis [Internet]. Ottawa: CADTH; 2015. [cited 2015 Dec 15]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/SR0421_cdr_complete_Entyvio_Nov-2-15_e.pdf

12. Clinical study report: M06-827. A multicenter, randomized, double-blind, placebo controlled study of the human anti-TNF monoclonal antibody adalimumab for the induction and maintenance of clinical remission in subjects with moderately to severely active ulcerative colitis [**CONFIDENTIAL** internal manufacturer's report]. Abbott Park (IL): Abbott Laboratories; 2012 Dec.

13. Molnar T, Farkas K, Nyari T, Szepes Z, Nagy F, Wittmann T. Response to first intravenous steroid therapy determines the subsequent risk of colectomy in ulcerative colitis patients. J Gastrointestin Liver Dis. 2011 Dec;20(4):359-63.

14. Mocciaro F, Renna S, Orlando A, Rizzuto G, Sinagra E, Orlando E, et al. Cyclosporine or infliximab as rescue therapy in severe refractory ulcerative colitis: early and long-term data from a retrospective observational study. J Crohns Colitis. 2012 Jul;6(6):681-6.

15. Gustavsson A, Halfvarson J, Magnuson A, Sandberg-Gertzen H, Tysk C, Jarnerot G. Long-term colectomy rate after intensive intravenous corticosteroid therapy for ulcerative colitis prior to the immunosuppressive treatment era. Am J Gastroenterol. 2007 Nov;102(11):2513-9.

16. Swenson BR, Hollenbeak CS, Koltun WA. Factors affecting cost and length of stay associated with the ileal pouch-anal anastomosis. Dis Colon Rectum. 2003 Jun;46(6):754-61.

17. Roberts SE, Williams JG, Yeates D, Goldacre MJ. Mortality in patients with and without colectomy admitted to hospital for ulcerative colitis and Crohn's disease: record linkage studies. BMJ [Internet]. 2007 Nov 17 [cited 2015 Dec 15];335(7628):1033. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2078633

18. Ontario Ministry of Health and Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto: The Ministry; 2015. [cited 2016 Jan 25]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/

19. Humira (adalimumab): 40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection [product monograph]. St-Laurent (QC): AbbVie Corporation; 2015 Jul 3.

20. [Pr]Simponi® (golimumab): Solution for injection 50 mg/0.5 mL 100 mg/1.0 mL [Pr]Simponi® I.V. (golimumab) solution for infusion 50 mg/4.0 mL [product monograph] [Internet]. Toronto (ON): Janssen Inc.; 2014 Nov 25. [cited 2016 Jan 12]. Available from: https://www.janssen.com/canada/sites/www_janssen_com_canada/files/product/pdf/sim11252014cpm_nc.pdf

21. [Pr]Remicade® (infliximab): Powder for solution, sterile, lyophilized, 100 mg/vial [product monograph] [Internet]. Toronto (ON): Janssen Inc.; 2015 Jul 22. [cited 2016 Jan 12]. Available from: https://www.janssen.com/canada/sites/www_janssen_com_canada/files/product/pdf/rmc07222015cpm_nc_183500.pdf

22. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76.

23. Ontario Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act: effective December 21, 2015 [Internet]. Toronto: The Ministry; 2015. [cited 2016 Jan 26]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html

24. Guide to interdisciplinary provider compensation. Toronto: Ontario Ministry of Health and Long-Term Care; 2010.

25. Collective agreement between: Ontario Nurses' Association (hereinafter referred to as the "Union") and: Sunnybrook Health Sciences Centre (hereinafter referred to as the "Hospital") [Internet]. Toronto: Ontario Nurses' Association; 2016. [cited 2016 Dec 16]. Available from: https://www.ona.org/documents/File/pdf/cas/hospitals/SunnybrookHealthSciencesCentre_March312016.pdf

26. Health Data Branch Web Portal. Toronto: Ministry of Health and Long Term Care. OCCI costing analysis tool; 2015

27. Italian Group for the Study of Inflammatory Bowel Disease, Armuzzi A, Biancone L, Daperno M, Coli A, Pugliese D, et al. Adalimumab in active ulcerative colitis: a "real-life" observational study. Dig Liver Dis. 2013 Sep;45(9):738-43.

28. Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2014 Apr;39(7):660-71.

29. Galvan-Banqueri M, Vega-Coca MD, Castillo-Munoz MA, Beltran CC, Molina LT. Indirect comparison for Anti-TNF drugs in moderate to severe ulcerative colitis. Farm Hosp [Internet]. 2015 Mar [cited 2015 Nov 16];39(2):80-91. Available from: http://www.aulamedica.es/fh/pdf/8218.pdf

30. Thorlund K, Druyts E, Toor K, Mills EJ. Comparative efficacy of golimumab, infliximab, and adalimumab for moderately to severely active ulcerative colitis: a network meta-analysis accounting for differences in trial designs. Expert Rev Gastroenterol Hepatol. 2015 May;9(5):693-700.

31. Archer R, Tappenden P, Ren S, Martyn-St James M, Harvey R, Besarir H, et al. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262) [ID695]. Sheffield, UK: University of Sheffield; 2014.

32. Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med. 2014 May 20;160(10):704-11.

33. Woehl A, Hawthorne AB. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis [abstract]. Gut. 2008;57 Suppl 2:A153.

34. Tsai HH, Punekar YS, Morris J, Fortun P. A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther. 2008 Nov 15;28(10):1230-9.

35. Woehl A, Hawthorne AB, Morgan C, Punekar Y, McEwan P. The epidemiology and healthcare resource use in patients with Crohn's disease: a population based UK study [abstract]. Value Health. 2007;10(6):A355.

36. Targownik LE, Singh H, Nugent Z, Bernstein CN. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. Am J Gastroenterol. 2012 Aug;107(8):1228-35.

37. Transparency committee opinion: Humira 40 mg, solution for injection in pre-filled syringe B/2 x 0.8 ml pre-filled glass syringes with 2 alcohol wipes (CIP code: 362 230-5) Humira 40 mg, solution for injection in pre-filled pen B/2 x 0.8 ml pens with 2 alcohol wipes (CIP code: 378 014-5) [Internet]. Paris: Haute Autorité de Santé; 2012 Oct 3. [cited 2016 Jan 12]. Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-07/humira_ct_12238.pdf

38. Humira[MC] -- Colite ulcéreuse [Internet]. Quebec (QC): INESSS; 2014 Oct. [cited 2016 Jan 12]. Available from: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Octobre_2014/Humira_CU_2014_10_CAV.pdf

39. Adalimumab, 40 mg/0.8 mL injection,0.8 mL cartridges and 0.8 mL syringes, Humira®- November 2013 [Internet]. Canberra (AU): Australian Government, Department of Health; 2013. Public Summary Document. [cited 2016 Jan 12]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-11/adalimumab

40. PTAC meeting held on 7 & 8 November 2013 (minutes for web publishing) [Internet]. Wellington (NZ): Pharmacology and Therapeutics Advisory Committee; 2013. [cited 2016 Jan 12]. Available from: https://www.pharmac.health.nz/assets/ptac-minutes-2013-11.pdf

41. Adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL cartridges; 40 mg/0.8 mL injection, 2 x 0.8 mL syringes; 40 mg/0.8 mL injection, 6 x 0.8 mL cartridges; 40 mg/0.8 mL injection, 6 x 0.8 mL syringes; Humira® AbbVie Pty Ltd [Internet]. Canberra (AU): Australian Government, Department of Health; 2015. Public summary document -- July 2015 PBAC meeting. [cited 2016 Jan 12]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-07/adalimumab-psd-jul-2015

42. July 2015 PBAC meeting PBAC outcomes -- subsequent decisions not to recommend [Internet]. Canberra (AU): Australian Government, Department of Health; 2015. [cited 2016 Jan 12]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-07/web-outcomes-july-2015-subsequent-decision-not-to-recommend.pdf

43. Adalimumab, 40 mg/0.8 mL injection, 2 x 0.8 mL cartridges and 2 x 0.8 mL syringes, 40 mg/0.8 mL injection, 6 x 0.8 mL cartridges and 6 x 0.8 mL syringes, Humira®, AbbVie Pty Ltd [Internet]. Canberra (AU): Australian Government, Department of Health; 2014. Public Summary Document- July 2014 PBAC Meeting. [cited 2016 Jan 12]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-07/adalimumab-psd-07-2014.pdf

44. July 2014 PBAC outcomes - subsequent decisions not to recommend [Internet]. Canberra (AU): Australian Government, Department of Health; 2014. [cited 2016 Jan 12]. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2014-07

45. November 2015 PBAC outcomes - subsequent decisions not to recommend [Internet]. Canberra (AU): Australian Government, Department of Health; 2015. [cited 2016 Jan 12]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2015-11/subsequent-decision-not-to-recommend-2015-11.pdf

46. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [Internet]. London: National Institute for Health and Care Excellence; 2015. [cited 2016 Jan 11]. (NICE technology appraisal guidance [TA329]). Available from: https://www.nice.org.uk/guidance/ta329

47. Swinburn P, Elwick H, Bean K, Curry A, Patel S. The impact of surgery on health related quality of life in ulcerative colitis. Gut [Internet]. 2012 [cited 2015 Dec 15];61 Suppl 2:A237. Available from: http://gut.bmj.com/content/61/Suppl_2/A237.2.full.pdf+html

48. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. Am J Med. 2003 Jan;114(1):39-43.

49. Odes S, Vardi H, Friger M, Esser D, Wolters F, Moum B, et al. Clinical and economic outcomes in a population-based European cohort of 948 ulcerative colitis and Crohn's disease patients by Markov analysis. Aliment Pharmacol Ther. 2010 Apr;31(7):735-44.

50. Hu D, Grossman D, Levin C, Blanchard K, Goldie SJ. Cost-effectiveness analysis of alternative first-trimester pregnancy termination strategies in Mexico City. BJOG. 2009 May;116(6):768-79.

51. Arseneau KO, Sultan S, Provenzale DT, Onken J, Bickston SJ, Foley E, et al. Do patient preferences influence decisions on treatment for patients with steroid-refractory ulcerative colitis? Clin Gastroenterol Hepatol. 2006 Sep;4(9):1135-42.

52. Smith KJ, Roberts MS. Quality-of-Life Utility Values for Erectile Function and Sildenafil Treatment. Clin Drug Investig. 2005;25(2):99-105.

53. Abdelrazeq AS, Kandiyil N, Botterill ID, Lund JN, Reynolds JR, Holdsworth PJ, et al. Predictors for acute and chronic pouchitis following restorative proctocolectomy for ulcerative colitis. Colorectal Dis. 2008 Oct;10(8):805-13.

54. Johnson P, Richard C, Ravid A, Spencer L, Pinto E, Hanna M, et al. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. Dis Colon Rectum. 2004 Jul;47(7):1119-26.

55. Krausz MM, Duek SD. Restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis and familial adenomatous polyposis: twenty years follow-up in 174 patients. Isr Med Assoc J. 2005 Jan;7(1):23-7.

56. Loftus EV, Jr., Friedman HS, Delgado DJ, Sandborn WJ. Colectomy subtypes, follow-up surgical procedures, postsurgical complications, and medical charges among ulcerative colitis patients with private health insurance in the United States. Inflamm Bowel Dis. 2009 Apr;15(4):566-75.

57. Gies N, Kroeker KI, Wong K, Fedorak RN. Treatment of ulcerative colitis with adalimumab or infliximab: long-term follow-up of a single-centre cohort. Aliment Pharmacol Ther. 2010 Aug;32(4):522-8.

58. Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology. 2015 May;148(5):1035-58.

59. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011 Jun;60(6):780-7.

60. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65.

61. Sandborn WJ, Colombel JF, D'Haens G, van Assche G, Wolf D, Kron M, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther. 2013 Jan;37(2):204-13.

62. Suzuki Y, Motoya S, Hanai H, Matsumoto T, Hibi T, Robinson AM, et al. Efficacy and safety of adalimumab in Japanese patients with moderately to severely active ulcerative colitis. J Gastroenterol [Internet]. 2014 Feb [cited 2015 Nov 16];49(2):283-94. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3925299

63. Punekar YS, Hawkins N. Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. Eur J Health Econ. 2010 Feb;11(1):67-76.

64. Poole CD, Connolly MP, Nielsen SK, Currie CJ, Marteau P. A comparison of physician-rated disease severity and patient reported outcomes in mild to moderately active ulcerative colitis. J Crohns Colitis. 2010 Sep;4(3):275-82.

65. Vaizey CJ, Gibson PR, Black CM, Nicholls R, Weston AR. Disease status, patient quality of life and healthcare resource use for ulcerative colitis in the UK: an observational study. Frontline Gastroenterology. 2014;5(3):183-9.

66. Johnson JA, Pickard AS. Comparison of the EQ-5D and SF-12 health surveys in a general population survey in Alberta, Canada. Med Care. 2000 Jan;38(1):115-21.