Common Drug Review
Pharmacoeconomic Review Report

October 2015

Drug	vedolizumab (Entyvio)
Indication	For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.
Listing request	As per indication
Manufacturer	Takeda Canada Inc.

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

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ABBREVIATIONS

CDR	CADTH Common Drug Review
CT	conventional therapy
IBD	inflammatory bowel disease
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
QALY	quality-adjusted life-year
TNF	tumour necrosis factor

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Vedolizumab (Entyvio)
Study Question	The objective of this project was to conduct a CUA to estimate the incremental cost-effectiveness of vedolizumab for adult patients (adult ≥ 18 years) with moderately to severely active UC who have had an inadequate response, loss of response to, or who were intolerant to either CT or infliximab
Type of Economic Evaluation	CUA
Target Population	Adult patients with moderately to severely active UC who have had an inadequate response, loss of response to, or who were intolerant to either CT or infliximab Subgroup analyses included: • Mixed population, includes both TNF alpha antagonist–naive and TNF alpha antagonist–failure patients, representing the ITT population of the vedolizumab trial (GEMINI-1) • TNF alpha antagonist–naive population • TNF alpha antagonist–failure population (both primary failure [no response] and secondary failure [loss of response after initially responding])
Treatment	Vedolizumab 300 mg infused intravenously over approximately 30 minutes at 0, 2, and 6 weeks (induction period), then every 8 weeks thereafter (maintenance period)
Outcomes	QALYs
Comparators	• Infliximab • CT
Perspective	Canadian publicly funded drug plans (Ontario Ministry of Health and Long-Term Care as a proxy)
Time Horizon	5 years
Results for Base Case	Mixed population: ICUR vs. CT = $60,196 TNF alpha antagonist–naive population: ICUR vs. CT = $56,107 TNF alpha antagonist–naive population: ICUR vs. infliximab = dominant TNF alpha antagonist–failure population: ICUR vs. CT = $65,607
Key Limitations	CDR identified the following key limitations: • Uncertainty regarding appropriate utility values • Uncertainty regarding cost and resource use Additional limitations were identified, but could not be addressed through CDR analyses, including: • Substantial uncertainty regarding the transition probabilities • Substantial uncertainty in the data for the maintenance phase • Uncertainty in the assessment point for vedolizumab; 6 weeks vs. 10 weeks • Exclusion of treatment waning • Limited time horizon
CDR Estimates	• The cost-effectiveness of vedolizumab versus TNF alpha antagonists is not known given uncertainty with the NMA, thus CDR focused on direct comparison with CT, which may not be the most appropriate comparator. • CDR was unable to test uncertainty on several parameters of interest given the structure of the model; specifically of note were the modelling of the transitions between health states • CDR reanalyses based on the key limitations (utility values, resource use) illustrated the sensitivity of the model to choices of parameters that could be modified: ICUR of $60,000 to $150,000 per QALY for vedolizumab vs. CT

CDR = CADTH Common Drug Review; CT = conventional therapy; CUA = cost-utility analysis; ICUR = incremental cost-utility ratio; ITT = intention-to-treat; NMA = network meta-analysis; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; UC = ulcerative colitis; vs. = versus.

EXECUTIVE SUMMARY

Background

Vedolizumab (Entyvio) is an integrin receptor antagonist indicated for adult patients (≥ 18 years) with moderately to severely active ulcerative colitis who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy (CT) or infliximab, a tumour necrosis factor (TNF) alpha antagonist.[1] Vedolizumab is available as a powder for concentrate for solution for infusion in a single-use 300 mg vial.[1] The recommended dose of vedolizumab, administered as an intravenous infusion over 30 minutes, is 300 mg at zero, two, and six weeks and then every eight weeks thereafter. The product monograph indicates that therapy should be discontinued in patients who show no evidence of therapeutic benefit by week 10.[1]

The manufacturer submitted a price of $3,290 per 300 mg vial, resulting in an annual per patient cost of $26,320 in year 1 and $21,385 in subsequent years. The manufacturer is requesting listing as per the Health Canada indication.

CADTH Common Drug Review (CDR) has previously reviewed adalimumab, infliximab, and golimumab for moderate to severe ulcerative colitis. CEDAC (Canadian Expert Drug Advisory Committee) recommended that infliximab not be listed, while CDEC (Canadian Drug Expert Committee) recommended golimumab not be listed at the submitted price.[2,3] The submission for adalimumab was withdrawn in the embargo period after the CDEC recommendation.[4] Infliximab has restricted or exceptional benefit access for ulcerative colitis in Ontario, Saskatchewan, Manitoba, Yukon, and the Non-Insured Health Benefits. Golimumab has an exceptional benefit access with the Non-Insured Health Benefits.

The manufacturer submitted a cost-utility analysis comparing vedolizumab with standard of care (CT: aminosalicylates, corticosteroids, and immunomodulators) or TNF alpha antagonist therapy for adult patients (≥ 18 years) with moderately to severely active ulcerative colitis who have had an inadequate response to, loss of response to, or were intolerant to either CT or infliximab. Although the primary analysis was on the mixed population of TNF alpha antagonist–naive and TNF alpha antagonist–experienced patients, subgroup analyses were also presented. The analysis used an initial decision-tree framework to represent the induction phase (six weeks) followed by a cohort health-state–transition Markov model structure to capture the maintenance over a five-year time horizon (with eight-week cycles) from the perspective of the public health care payer. The manufacturer reported that for a mixed population, vedolizumab was associated with an incremental cost-utility ratio (ICUR) of $60,196 per quality-adjusted life-year (QALY) when compared with CT.

Summary of Identified Limitations and Key Results

CDR identified several limitations with the manufacturer's model. The key assumptions that could not be accounted for by CDR relate to the lack of comparative clinical information and issues with the economic model in how patients transition to the various health states.

Although the manufacturer conducted a network meta-analysis to assess the comparative clinical effects of vedolizumab compared with infliximab, golimumab, and adalimumab, there was substantial heterogeneity due to the substantial differences in the maintenance phases of the studies, thus the point estimates for the long-term comparative effectiveness are uncertain. CDR clinical reviewers

concluded that it was unclear whether vedolizumab is as efficacious as the other TNF alpha drugs in maintaining treatment effect.

The manufacturer modelled the transition of patients through the various health states using an unconventional approach. CDR attempted to examine this issue based on data provided by the manufacturer from GEMINI-1 but encountered some challenges when trying to incorporate this information into the model, which led to incongruous results. As such, alternate estimates could not be used to test the validity of the manufacturer's approach.

CDR tested the limitations regarding utility values, surgery, and adverse event rates, costs, and resource use, resulting in an ICUR ranging from $60,000 to $150,000 per QALY for vedolizumab compared with CT.

Other limitations identified, which CDR was unable to account for, included uncertainty in the appropriateness of the clinical data from the maintenance phase of the GEMINI-1 clinical trial to inform the model; differences in the assessment point for vedolizumab — a six-week induction period was considered in the manufacturer's pharmacoeconomic submission while the vedolizumab product monograph indicates that patients who show no evidence of therapeutic benefit by week 10 should discontinue therapy, potentially allowing for a further four weeks of treatment and assessment; and increasing the time horizon beyond five years given the chronic nature of the condition, which would incorporate further uncertainty into the model.

Conclusions

CDR identified several key limitations with the manufacturer's submission that could not be examined through reanalyses, including a lack of comparative clinical information and issues with the transition probabilities used in the model. These limitations result in significant uncertainty regarding the cost-effectiveness of vedolizumab. For parameters that could be assessed, the results varied significantly, with the ICUR ranging from $60,000 to $150,000 per QALY.

At a dose of 300 mg every eight weeks, the cost of vedolizumab in year 1 ($26,320) and subsequent years ($21,385) is lower than infliximab ($31,602 and $25,677, respectively) but higher than golimumab ($22,803 and $19,763, respectively).

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing vedolizumab with standard of care, defined as conventional therapy (CT) (aminosalicylates, corticosteroids, and immunomodulators) or tumour necrosis factor (TNF) alpha antagonist therapy (infliximab, adalimumab, golimumab) for adults (≥ 18 years) with moderately to severely active ulcerative colitis who have had an inadequate response to, loss of response to, or were intolerant to either CT or infliximab over a five-year time horizon. The analysis included an initial decision-tree to capture the induction phase of treatment, and a cohort health-state–transition Markov model structure to capture the maintenance phase of treatment. The health states in the Markov model were remission, mild disease, moderate to severe disease, surgery, post-surgery remission, post-surgery complications, discontinuation, and death. In the decision-tree induction phase, patients initiate treatment with biologic drug therapy (vedolizumab, adalimumab, golimumab, or infliximab) or CT, or they receive surgery. At the end of the six-week induction phase, patients who respond (based on a decrease in Mayo score of 3 or more [30% or more] from baseline) enter the Markov model in either the remission or mild health state and receive biologic drug therapy, CT, or surgery. Patients who fail to respond biologic drug therapy during the induction phase or who discontinue due to adverse events enter the Markov model in the moderate to severe health state and receive CT. Patients who fail a biologic drug move to CT or surgery. Patients who enter the decision-tree model in the surgery group immediately move to the surgery portion of the Markov structure.

In the Markov model, patients may transition every eight weeks (cycle-time). The model is driven by transition probabilities. The probability of transitioning to another health state depends on both the current health state and current treatment. Data for the transition probabilities for biologic drugs and CT differ between the treatments and are based on data from the GEMINI-1 trial[5] (for vedolizumab and CT) and the network meta-analysis (NMA) (for the other biologic drugs). Health state utility values are based on the results of a published US article that obtained utility values through an interview of patients using the time-trade off method,[6] although several other sources of utility values were tested in sensitivity analyses. Disutility values for adverse events were based on several sources from the published literature.[7-11] Costs for drug acquisition are based on information from the manufacturer as well as the Ontario Drug Benefit Formulary.[12] Costs and resource use associated with drug administration (physician visits, hospitalization, laboratory tests, surgery) are stratified based on health state and are derived from Canadian data sources.[13]

The analysis is conducted from the perspective of the public health care payer.[13] The model is designed so that results are available at only one time for vedolizumab compared with one other treatment (CT or biologic drug); it does not allow comparison of all treatment options simultaneously.

2. MANUFACTURER'S BASE CASE

The manufacturer reported that in the mixed population, vedolizumab was associated with an incremental cost-utility ratio (ICUR) of $60,196 per quality-adjusted life-year (QALY) when compared with CT.[13]

In the TNF alpha–naive population, the manufacturer reported the following ICURs for vedolizumab:

- $56,107 versus CT
- dominant versus infliximab.

In the TNF alpha– failure population, the manufacturer reported the following ICURs for vedolizumab:

- $65,607 versus CT.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer tested uncertainty for several parameters through both probabilistic and deterministic sensitivity analyses. The deterministic sensitivity analysis found the model results to be relatively stable, but noted that time horizon and health state utility had large impacts on the model's incremental cost-effectiveness ratio (ICER).

The probabilistic sensitivity analysis was conducted as a second-order Monte-Carlo simulation over 3,000 iterations. The manufacturer reported that the mean probabilistic ICER from the 3,000 iterations was $61,770, similar to the deterministic result. The manufacturer's cost-effectiveness acceptability curve for vedolizumab compared with CT for the mixed population indicated that at a willingness-to-pay threshold of $50,000/QALY, vedolizumab had a 10% chance of being cost-effective, and at a willingness-to-pay threshold of $75,000/QALY, vedolizumab had an 89% chance of being cost-effective.

The manufacturer undertook exploratory analyses comparing vedolizumab with adalimumab (in the mixed, TNF alpha–naive, and TNF alpha–failure populations) and golimumab (in the TNF alpha–naive population). The exploratory analyses reported the ICURs for vedolizumab as follows:

- $38,819 versus adalimumab (mixed population)
- $44,266 versus adalimumab (TNF alpha–naive population)
- $50,355 versus golimumab (TNF alpha–naive population)
- $37,189 versus adalimumab (TNF alpha–failure population).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CDR identified the following limitations with the manufacturer's model that were important and could be addressed in CDR's reanalysis:

a. **Uncertainty regarding appropriate utility values.** The manufacturer presented six different sources of utility data in its analysis,[6,14-18] with large variance in values. In the base case, the manufacturer used published values. There was no appropriate justification for its choice of utility data for the base-case analysis, especially as the manufacturer collected utility data in the GEMINI clinical trial and presented these in a sensitivity analysis. CDR considered that these values should have been used in the base-case analysis.

b. **Inappropriate methods to derive disutility estimates.** The manufacturer used disutility estimates based on published literature that were not in the ulcerative colitis population, and the inverse utility values for health states to estimate disutility. CDR considered this inappropriate and removed the disutility estimates from the reanalysis.
c. **Surgery rate assumptions.** The use of a constant surgery rate, transformed from published literature, potentially overestimates the probability of surgery and time spent in post-surgery complications over the model's time horizon, resulting in increased costs and reduced health gains with surgery. The probability of repeat surgery and complications would be expected to be greater in the first 12 months after surgery rather than remaining constant indefinitely. CDR undertook reanalysis reducing the rate of surgery.
d. **Health state costs and resource use.** There is uncertainty regarding costs and resource use estimated for each of the health states. The CDR clinical expert indicated there had been changes to physician reimbursement, and assumptions around visits may have been overestimated.
e. **CT costs**. The manufacturer assumed that all patients on a biologic drug would receive half the amount of CT that patients not on a biologic drug would receive. The CDR clinical expert did not consider an assumption of 50% CT use appropriate. CDR undertook reanalyses assuming 100% CT use for both sets of patients.
f. **Appropriateness of adverse event rates for CT.** Patients in the placebo group of the GEMINI-1 trial (used to inform the CT group of the model) were given a sham infusion to maintain blinding. As patients receiving CT would not receive a sham injection, it is unlikely that they would have as many skin reactions as were seen in the clinical trial.

The following key limitations could not be tested given the available data and structure of the model:

- **Calculation of transition probabilities.** There is substantial uncertainty regarding the transition probabilities for the maintenance phase, and the methodology used to calculate them does not represent a conventional approach. In response to CDR's request, the manufacturer provided data on the proportion of patients in the remission, mild, moderate to severe, and surgery health states from baseline to the end of induction period, and from the start to the end of the maintenance phase, from GEMINI-1[19] and attempted to provide justification of the optimization procedure. CDR found that uncertainty existed given the transition probabilities based on the clinical trial compared with the transition probabilities used in the model.
- **Uncertainty with the manufacturer-submitted NMA.** There was substantial heterogeneity due to the substantial differences in the maintenance phases of the studies, thus the point estimates for the long-term comparative effectiveness are uncertain. CDR clinical reviewers concluded that it was uncertain whether vedolizumab is similarly efficacious to the other TNF alpha drugs in maintaining treatment effect. Therefore, under the assumption of equivalent efficacy, as per the CDR cost table, using vedolizumab every eight weeks would result in a lower annual drug acquisition cost than for infliximab, but higher than for golimumab.
- **Uncertainty with the applicability of maintenance phase data to the NMA.** Use of data from the maintenance phase of the GEMINI-1 clinical trial is uncertain given the methods and randomization used for patients included in the maintenance phase of the trials of the comparator treatments.
- **Differences in assessment point for vedolizumab.** The assessment point for vedolizumab in the economic model was at six weeks. The product monograph indicates that patients who show no evidence of therapeutic benefit by week 10 should discontinue therapy, which differs from both the study end point and the submitted model. CDR was not able reassess the impact of this factor, given the model structure and data limitations.

- **Short time horizon.** Although the manufacturer's five-year time horizon is consistent with the time horizon used in the CADTH health technology assessment of drugs for inflammatory bowel disease (IBD),[20] the CDR clinical expert stated that ulcerative colitis is a chronic condition and ideally would involve a lifetime horizon. CDR did not undertake reanalyses to lengthen the time horizon because, the way the model is structured, extending the time horizon would increase uncertainty in other parameters of the model.
- **The manufacturer did not include treatment waning in its analysis.** Given the model structure, CDR was unable to reanalyze to test this assumption.

5. CADTH COMMON DRUG REVIEW ANALYSES

Given the issues identified with the results of the NMA and the transition probabilities used in the model, reanalyses for the comparison of vedolizumab against infliximab, adalimumab, and golimumab were not undertaken.

CDR tested the limitations individually, which resulted in ICURs for vedolizumab compared with CT ranging from approximately $60,000 per QALY to approximately $138,000 per QALY. CDR also undertook an analysis combining the key limitations; the results indicated that the ICUR for vedolizumab compared with CT was approximately $150,000 per QALY.

TABLE 2: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of Vedolizumab Versus CT		
Price of Vedolizumab	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR**
Submitted ($3,290)	$60,196	$149,581
10% reduction ($2,961)	$52,166	$131,084
20% reduction ($2,632)	$44,137	$112,587
30% reduction ($2,303)	$36,107	$94,090
40% reduction ($1,974)	$28,077	$75,593
50% reduction ($1,645)	$20,047	$57,096
60% reduction ($1,316)	$12,018	$38,599
70% reduction ($987)	$3,988	$20,102

CDR = CADTH Common Drug Review; CT = conventional therapy; ICUR = incremental cost-utility ratio.

With a price reduction of approximately 27%, the ICUR for vedolizumab compared with CT would fall below $100,000 per QALY based on the CDR combined analysis. A price reduction of approximately 54% would be required for the ICUR to fall below $50,000 per QALY.

6. ISSUES FOR CONSIDERATION

- In the manufacturer's economic submission, vedolizumab is analyzed at a dose of 300 mg every eight weeks as recommended in the product monograph.[1] It is noted that a cohort of patients in GEMINI-1 received vedolizumab 300 mg every four weeks, which is not specifically addressed (recommended or not recommended) in the product monograph. There is a potential for patients who do not initially respond to receive more frequent doses of vedolizumab.
- The CDR clinical expert indicated the possibility for off-label use in patients with Crohn disease.
- The CDR clinical expert stated that even if patients respond to a biologic drug and go into remission, based on the initial experience with other biologic drugs, patients may remain on chronic long-term treatment to maintain remission.
- The manufacturer indicated that it has a patient support program in place that covers the administration of vedolizumab. If this patient support program is not operationalizable to the participating plans, the total costs associated with vedolizumab may be underestimated, leading to a higher ICUR.

7. PATIENT INPUT

Input was received from two patient groups, Crohn's and Colitis Canada and the Gastrointestinal Society. The responses highlighted two keys concerns for patients with IBD: the lack of control over bowel movements (including the urgent and frequent need of a bathroom), and a fear of flare-ups and the desire for sustained remission, which has been suggested to be more important than relieving any one symptom of IBD. Patients with IBD reported severe impact on quality of life. A large majority of surveyed patients indicated preference for a biologic drug, despite its potential risks and side effects, over surgery. The manufacturer's economic submission reported quality of life data sourced directly from the GEMINI-1 clinical study within a sensitivity analysis.

8. CONCLUSIONS

CDR identified several key limitations with the manufacturer's submission that could not be examined through reanalyses, including a lack of comparative clinical information and issues with the transition probabilities used in the model. This results in significant uncertainty regarding the cost-effectiveness of vedolizumab. For parameters that could be assessed, the results varied significantly, with the ICUR ranging from $60,000 to $150,000 per QALY in the mixed population (treatment-naive and treatment-experienced).

At a dose of 300 mg every eight weeks, the cost of vedolizumab in year 1 ($26,320) and subsequent years ($21,385) is lower than that of infliximab ($31,602 and $25,677, respectively) but higher than that of golimumab ($22,803 and $19,763, respectively).

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.

TABLE 3: COST COMPARISON TABLE FOR BIOLOGIC DRUGS FOR ULCERATIVE COLITIS

Drug or Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Annual Drug Cost ($)
Vedolizumab (Entyvio)	300 mg/vial	Powder for concentrate for solution for infusion	3,290.00[a]	300 mg at weeks 0, 2, and 6, then every 8 weeks thereafter	Year 1: 26,320; thereafter: 21,385
Adalimumab (Humira)[b]	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: 22,210; thereafter: 19,249
Golimumab (Simponi)[b]	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)	100 mg/10 mL	Vial for IV Infusion	987.56	5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter[c]	Year 1: 31,602; thereafter: 25,677

IV = intravenous.
[a] Manufacturer-submitted price.
[b] Golimumab and adalimumab are not currently reimbursed by any formulary for ulcerative colitis, although they both have Health Canada approval for this indication. Given CADTH Common Drug Review recommendations, where these treatments are listed for this indication, the actual price may be lower than the publicly listed price.
[c] Assumes 80 kg patient.
Note: All prices are from the Ontario Drug Benefit Formulary Exceptional Access Program (accessed May 2015) unless otherwise indicated and do not include dispensing fees.

TABLE 4: OTHER TREATMENTS FOR ULCERATIVE COLITIS

Drug or Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Average Daily Drug Cost ($)	Average Annual Cost ($)
Aminosalicylates						
5-ASA (Asacol, Asacol 800)	400 mg	Tablet	0.3951	Active: 0.8 g to 3 g daily in divided doses Maint: 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	Tablet	0.3951	Active mild or moderate: 2 tabs to 8 tabs in divided doses (max or severe: 12 tabs daily) Maint: 4 tabs in divided doses	0.79 to 4.74 1.58	288 to1,731 577
5-ASA (Mesasal)	500 mg	Ent. tab	0.6368	Active: 1.5 g to 3 g tabs daily in divided doses Maint: 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- or extended-release tab	1.6253	Induction: 2 tabs to 4 tabs once daily Maint: 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	1.2603 1.8887	Supp: 1 g to 1.5 g daily	1.89 to 3.78	689 to 1,379
	2 g/60 g 4 g/60 g	Rect susp.	4.1500[a] 7.0351	Active: 4 g nightly Maint: 2 g nightly or 4 g every two nights	7.04 3.52 to 4.15	2,568 1,287 to 1,515
Olsalazine (Dipentum)	250 mg	Capsule	0.5330	Active: 1 g to 3 g daily in divided doses Maint: 1 g daily in divided doses	2.13 to 6.40 2.13	778 to 2,335 748
Sulfasalazine (Salazopyrin and generic)	500 mg 500 mg	Tablet Ent. tab	0.1804 0.2816	Active: 1 g to 2 g three to four times daily Maint: 1 g two to three times daily	1.08 to 4.51 0.72 to 1.69	395 to 1,645 263 to 617

Drug or Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Average Daily Drug Cost ($)	Average Annual Cost ($)
Immunosuppressants						
6-mercaptopurine (Purinethol and generic)	50 mg	Tablet	2.8610	50 mg to 100 mg daily	2.86 to 5.72	1,044 to 2,088
Azathioprine (Imuran and generic)	50 mg	Tablet	0.2405	2.5 mg/kg daily	0.96[b]	351
Corticosteroids, Topical						
Betamethasone enema (Betnesol)	5 mg/100 mL	Enema	10.1457	5 mg nightly	10.15	3,703
Budesonide (Entocort)	0.02 mg/mL	Enema (100 mL)	8.5200[a]	2 mg nightly	8.52	3,110
Hydrocortisone enema (Cortenema)	100 mg/60 mL	Enema	7.2711	60 mL nightly or every other night	3.64 to 7.27	1,327 to 2,654
(Cortifoam)	15 g/pack (14 doses)	Rectal aerosol	88.9200	One dose nightly or every other night	3.18 to 6.35	1,159 to 2,318
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 (generic)	1 mg 5 mg 50 mg	Tablet	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; Ent. tab = enteric-coated tablet; IV = intravenous; Maint = maintenance; max = maximum; NA = not applicable; Rect. susp = rectal suspension; Supp = suppository; tab = tablet.

[a] Saskatchewan Formulary (May 2015).

[b] Assumes 80 kg patient and vial wastage if applicable.

Note: All prices are from the Ontario Drug Benefit Formulary (May 2015) unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS VEDOLIZUMAB RELATIVE TO CONVENTIONAL THERAPY BASED ON THE MANUFACTURER'S SUBMISSION?

Vedolizumab vs. Conventional Therapy	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	$60,196 per QALY (mixed population) $56,107 per QALY (TNF alpha–naive population) $65,607 per QALY (TNF alpha–experienced population)					

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

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS VEDOLIZUMAB RELATIVE TO INFLIXIMAB BASED ON THE MANUFACTURER'S SUBMISSION?

Vedolizumab vs. infliximab	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	Vedolizumab dominates infliximab (TNF alpha–naive population)					

CE = cost-effectiveness; NA = not applicable; TNF = tumour necrosis factor; vs. = versus.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	Discussion and justification of the calibration process for the transition probabilities was lacking and given the transition probabilities drove the model, this was a large issue.		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 8: AUTHOR INFORMATION

Authors	Affiliations
[redacted]	[redacted]

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

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

	NICE	SMC	PBAC[a]
Date of Publication	March 2015	May 2015	July 2014[b] March 2015[b]
Drug	300 mg vial	300 mg for infusion	Injection, 1 × 300 mg vial
Price	£2,050 per 300 mg vial	Vial price not reported, but back calculated to £2,050 per 300 mg vial	Confidential
Treatment	300 mg IV infusion at 0, 2, and 6 wks then every 8 wks. Discontinuation of therapy considered if no evidence of therapeutic benefit by week 10.		
Comparators	CT, INF, ADA, GOL	CT Exploratory analysis: INF, ADA, GOL	SOC (5-ASA, corticosteroids, immunomodulators) Supplementary comparators: ADA, GOL, INF
Population Modelled	• Adults, moderate to severe UC, inadequate response or lost response or intolerant to CT or TNF alpha • TNF alpha–naive • TNF alpha–experienced	Primary analysis: moderate to severe UC, inadequate response or lost response or intolerant to CT or TNF alpha Scenario analysis: TNF alpha–naive	Moderate to severe UC
Time Horizon	10 y	Lifetime (treated for 2 y)	30 y
Cycle Length	Induction: 6 wks Maintenance: 8 wks	Decision-tree: 6 wks Markov: 8 wks	First cycle: 10 wks Subsequent: 8 wks
Discount Rate	3.5%	Not stated	Not stated
Type of Model	CUA: Decision-tree for induction; Markov for maintenance. 3 health states on Mayo scores (remission, mild, moderate to severe), surgery, 2 post-surgical states, discontinuation, death	CUA: Decision-tree for 6-week induction; Markov model with 6 health states: remission, mild UC, moderate to severe UC, surgery, post-surgery and post-surgery complications, death	CUA: 10 health states, remission (VED or PL), mild to moderate (VED or PL), moderate to severe (VED or PL), surgery, post-surgery remission, post-surgery complications, death
Key Outcomes	QALYs, response	QALYs	QALYs, response

	NICE	SMC	PBAC[a]
Results	Full population: • VED dominated surgery • £33,297/QALY (VED vs. CT) TNF alpha inhibitor–naive: • VED dominated INF, GOL, surgery • £6,634/QALY (VED vs. ADA) • £4,862/QALY (VED vs. CT) TNF alpha inhibitor–experienced: • VED dominated surgery • £64,999/QALY (VED vs. CT) **ERG analyses:** Surgery may not be an acceptable option, thus: • Full population: £53,084/QALY vs. CT • TNF alpha–naive: VED dominated by ADA • TNF alpha–experienced: £48,205/QALY vs. CT Committee considered: • Limit 2 subpopulations • 1-y stopping rule for biologic drugs • Revised utility values • TNF alpha–naive, ADA dominated VED; and £53,000/QALY VED vs. CT • Revised utility estimates and 1-y stopping rule, < £20,000/QALY to dominant • TNF alpha–experienced, £27,500 to £37,000/QALY VED vs. CT	Full population: • Including patient access scheme (PAS): £28,429/QALY VED vs. CT • At list price: £45,191 • PSA indicated that at WTP threshold of £30,000, 60% probability VED cost-effective TNF alpha–naive: • £24,124/QALY VED vs. CT (with PAS) • At list price: £39,489 vs. CT • VED (with PAS) dominated INF, GOL; £5,670 vs. ADA Committee: • Lower surgery rate (2.45%): £33,833/QALY VED (PAS) (£29,561 in TNF alpha–naive) • Higher surgery rate (8.2%): £25,008 and £20,673, respectively • Reduce complication rate by 40%: £29,623/QALY VED (PAS) (£25,232 in TNF alpha–naive) • Lower cost of complications, £35,715/QAL VED (PAS) (£31,377 TNF alpha–naive) • Revised induction period, £30,262 VED (PAS) (£26,393 TNF alpha–naive) • Combining lower surgery rate and revised induction period, £35,852 VED (PAS) (£32,051 TNF alpha–naive) • Use 1 y/3 y tx £22,106/£30,812 VED (PAS) (£16,486/£27,924 TNF alpha–naive)	• $15,000 to $45,000/ QALY • Committee considered ICER was likely underestimated • Committee noted a multi-variate analysis with a 10-y TH, utility values and VED tx duration of 7.3 y resulted in $75,000 to $105,000/QALY
Sources of Uncertainty	• Lifetime TH preferred • Uncertainty in calculation and calibration processes for transition probabilities • Plausibility of transition probabilities for surgery • Marketing authorizations did not stipulate stopping rules, while company assumed responders switch to CT after 1 y	• Rate of surgery of 4.9% over 1 y was applied every year; this figure may overestimate likely rates of surgery • Rate of complications seen in the initial months post-surgery maintained over the long term resulting in high rate of unplanned procedures	2014: • Results sensitive to model TH, tx duration, efficacy for VED non-responders, utility values • BSC more relevant comparator • Concern design of GEMINI-1 potentially favours VED • ITC of INF vs. VED similar

	NICE	SMC	PBAC[a]
	• Continue biologic drug for full year even if effect lost after induction — not realistic • EQ-5D data from GEMINI-1 appropriate • Post-surgery remission utility value lower than moderate to severe UC not plausible, underestimated effect of surgery • AEs for CT based on trial where patients given PL transfusion or injection — not actual practice • Some costs excluded or dated	• Concern cost of surgery complications may have been overestimated • Different induction dosing regimen for VED than recommended • Concerned about weaknesses with NMA and thus did not conduct any revised analyses against the TNF alpha antagonists	response rate • No comment made on ITC of VED vs. ADA • PBAC did not accept non-inferiority VED vs. INF for safety; therefore no basis for CMA
Recommendation	VED recommended as an option, within its marketing authorization, for treating moderately to severely active UC in adults if price discount can be agreed in PAS	• VED accepted for use in NHS Scotland • Patients reassessed at least every 12 months to determine if still clinically appropriate • People in complete remission at 12 months: consider stopping VED, resume if relapse • Advice contingent on PAS in NHS Scotland/list price equivalent or lower	2014: • PBAC rejected VED: Non-inferiority of VED vs. INF — CMA not supported • CE of VED vs. placebo too high • CE of listing VED post-tx failure with 5-ASA, oral immunosuppressives/TNF alpha unknown 2015: • PBAC recommended VED on cost-min basis vs. INF • PBAC considered equi-effective doses: VED 300 mg wks 0, 2, 6 then every 8 wks = INF 5 mg/kg at wks 0, 2, 6 then every 8 wks
CDR Assessment	Economic evaluation submitted to CDR similar to NICE and SMC, but slightly different from submission to PBAC. Similar limitations identified by NICE, SMC, and PBAC; PBAC found VED was not inferior to INF.		

5-ASA = 5-aminosalicylic acid; ADA = adalimumab; AE = adverse event; BSC = best supportive care; CE = cost-effectiveness; CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; CT = conventional therapy; CUA = cost-utility analysis; EQ-5D = EuroQol 5-Dimensions Questionnaire; GOL = golimumab; ICER = incremental cost-effectiveness ratio; INF = infliximab; ITC = indirect treatment comparison; IV = intravenous; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PAS = patient access scheme; PL = placebo; QALY = quality-adjusted life-year; SMC = Scottish Medicines Consortium; SOC = standard of care; TH = time horizon; TNF = tumour necrosis factor; tx = treatment; UC = ulcerative colitis; VED = vedolizumab; vs. = versus; wks = weeks; WTP = willingness to pay; y = year.

[a] Data for PBAC were reported based on the submission for the July 2014 meeting, with mention of the summary recommendation text from the March 2015 meeting. No public summary document was available at the time this report was written; therefore, additional text pertaining to that recommendation was not available.

[b] Publication date not stated; date of meeting used instead.

Note: In March 2015, the currency conversion from £ to C$ was approximately 1.89:1.

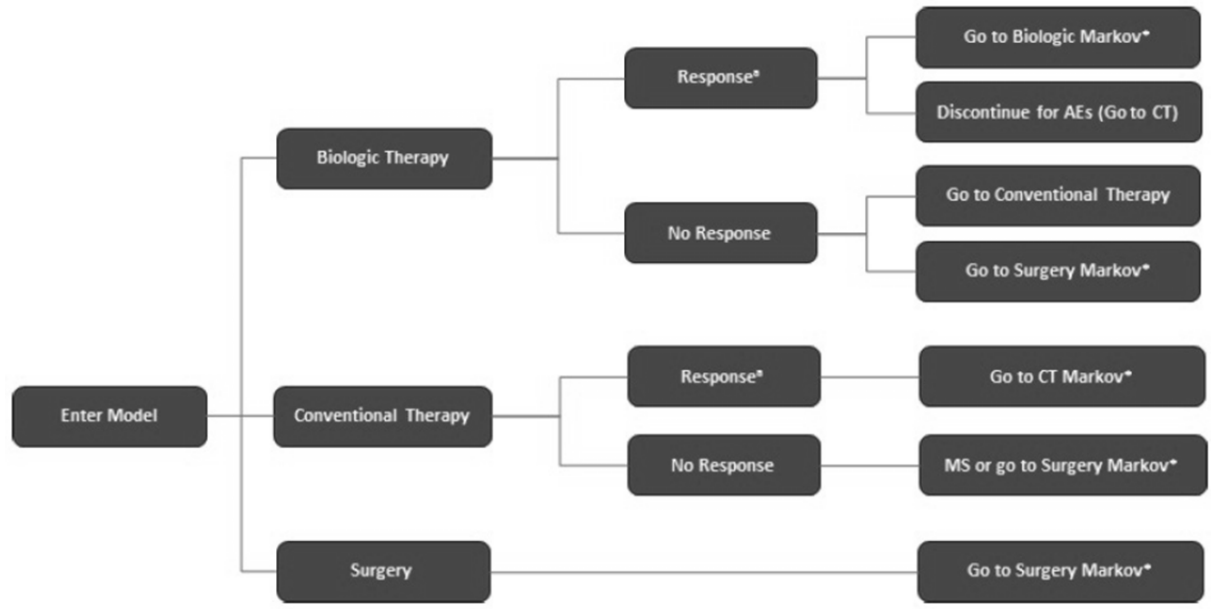
APPENDIX 5: REVIEWER WORKSHEETS

1. Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis from the perspective of Canada's publicly funded drug plans,[13] which included an initial decision-tree to capture the induction phase of treatment and a cohort health-state–transition Markov model structure to capture the maintenance phase of treatment. The model was developed by RTI Health Solutions for Takeda Pharmaceuticals International Inc. and was adapted to the Canadian setting according to current Canadian guidelines. The manufacturer stated that the model structure was based on the National Institute for Health and Care Excellence (NICE) submission for infliximab for subacute manifestations of ulcerative colitis and a publication by Tsai et al.[14,21]

In the decision-tree induction phase, patients initiate treatment with one of the biologic drug therapies (vedolizumab, adalimumab, golimumab, or infliximab) or conventional therapy (CT), or they receive surgery (Figure 1). At the end of the six-week induction period, patients then proceed to one of several states based on their initial response to treatment in the Markov model (Figure 2). Patients who enter the decision-tree model in the surgery group immediately move to the surgery portion of the Markov structure.

FIGURE 1: DECISION-TREE SCHEMATIC FOR INDUCTION PHASE



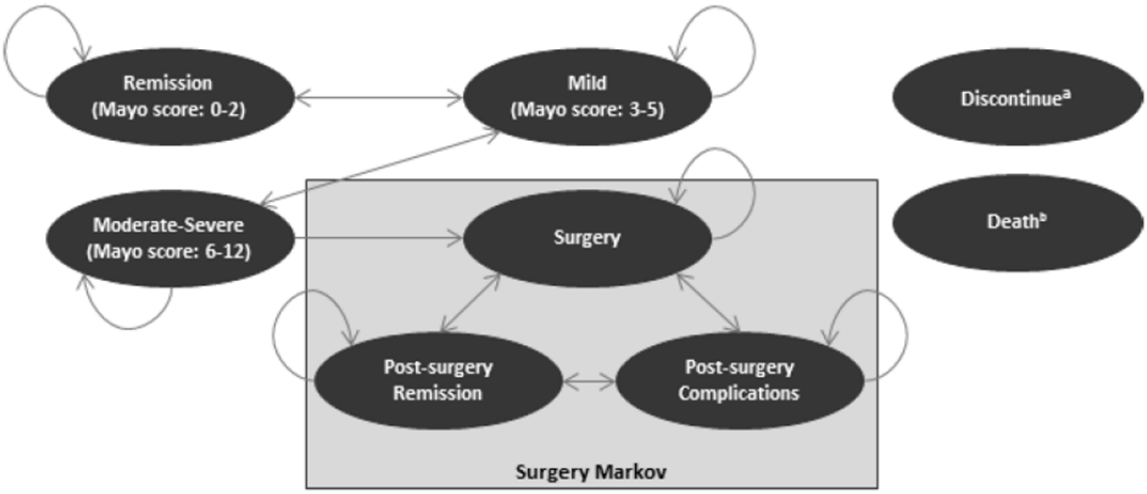
AE = adverse event; CT = conventional therapy; MS = moderate to severe.
[a] Response defined as drop in Mayo score ≥ 3; includes patients who achieve remission (remission = subset of response). Remission defined as Mayo score < 3.
* Markov structure can be seen in Figure 2. Structure for biologic drug therapies and CT are similar; differences arise with transition probabilities. Surgery Markov is a subset of the Markov for biologic drugs and conventional therapy.
Source: Manufacturer's Pharmacoeconomic Report, page 24.[13]

A model structure where patients who fail a tumour necrosis factor (TNF) alpha antagonist would then receive CT was considered reasonable, as no province currently reimburses two TNF alpha antagonists for the treatment of moderately to severely active ulcerative colitis (that is, no sequential use of TNF alpha antagonists). However, sequential TNF alpha antagonist use is explored in sensitivity analyses.

In the decision-tree, response is defined as a drop in Mayo score of 3 points or more. Patients who fail to respond to biologic drug therapy during the induction phase or who discontinue due to adverse events enter the Markov model in the moderate to severe health state. Responders in the induction phase decision-tree enter the Markov model in either the remission or mild health state.

The Markov surgery structure was reported to be consistent with previously published health economic modelling approaches.[14,21] The CADTH Common Drug Review (CDR) clinical expert indicated that the reported health states were appropriate. Following surgery, these patients may subsequently experience post-surgical complications, require additional surgeries, or remain in post-surgical remission (Figure 2).

FIGURE 2: MARKOV MODEL SCHEMATIC FOR MAINTENANCE PHASE



[a] Reasons for discontinuation include lack of response and adverse events. Discontinuation due to adverse event is only applicable to responders on biologic drugs; non-responders on biologic drugs switch to conventional therapy and continue receiving it until the model end or patient requires surgery.
[b] Patients may transition to death from any health state during any cycle.
Source: Manufacturer's Pharmacoeconomic Report, page 26.[13]

In the Markov model, patients transition every eight weeks (cycle-time). The probability of transitioning to another health state depends on both the current health state and the current treatment. Patients on a biologic drug who transition to the moderate-severe health state can remain in that state for a maximum of one year, after which they will discontinue due to lack of response and switch to CT. Data for the transition probabilities for biologic drugs or CT were based on data from the GEMINI-1 clinical trial and the manufacturer-supplied network meta-analysis (NMA), and differed between the treatments. The model is driven by the transition probabilities.

Data from the induction phases of the clinical studies included in the manufacturer's NMA[5,22-26] inform the proportion of patients in each health state prior to the initiation of the maintenance phase; while data from the maintenance phase (from week 6 to week 52) of the clinical trials were used to inform the rest of the transitions for year 1 and subsequent years.[5,22-24,26,27] The transition probabilities for the maintenance phase were stated to have been optimized to minimize deviation between the proportion of patients in the remission and mild health states within the Markov calculation at year 1 and the actual data from the clinical trial. The manufacturer stated that a "starting solution" was used; a calibration (or

"optimization") process based on data derived from the GEMINI-1 trial and NMA was applied to the starting solution using Microsoft Excel Solver. No justification for values used in the starting solution was provided.

Patients who fail a TNF alpha antagonist move to CT or surgery. Use of subsequent TNF alpha antagonists was not addressed directly in the model structure but through the selection of a TNF alpha antagonist–failure population.

TABLE 9: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Comparison vs. CT: GEMINI-1 Comparison vs. biologic drugs: manufacturer-sponsored NMA	The CDR Clinical Review of the NMA concluded due to the substantial differences in the maintenance phases of the studies, the point estimates for the long-term comparative effectiveness are uncertain; thus it remains unclear whether these drugs are similarly efficacious in maintaining remission and response.
Mixed population	GEMINI-1 (CT) and NMA (vedolizumab, adalimumab, and CT)	
TNF alpha–naive population	GEMINI-1 (CT) and NMA (vedolizumab, infliximab, golimumab, adalimumab, and CT)	
TNF alpha–failure population	GEMINI-1 (CT) and NMA (vedolizumab, adalimumab, and CT)	
Discontinuation	CSR C13006 (GEMINI-1), Rutgeerts et al. 2005,[22] Reinisch et al. 2011,[23] Sandborn et al. 2012,[24] Sandborn et al. 2014,[25] and Suzuki et al. 2014[26] Discontinuation split by phase of treatment: induction, maintenance	Reasons for discontinuation: lack of initial response, loss of response, AEs. Due to the differences in study designs, the assumption of discontinuations in the maintenance phase is highly uncertain.
Transition Probabilities		
Drugs	Data from the induction and maintenance phases of GEMINI-1 and NMA were used for transition probabilities of relevant comparators based on an unjustified starting solution.	As noted in the review of the efficacy information, the transition estimates for the biologic drugs based on the NMA are uncertain. CDR found substantial uncertainty with the methods used to determine the final transition probabilities used: no justification was provided for the starting solution in the submission. The manufacturer indicated it calibrated and optimized the transition probabilities. The process of calibration and optimization of the starting solution values was not appropriately justified.
Surgery	Published literature	Probability of repeat surgery converted from 6-month estimates to 8-weekly (assuming a constant rate), then applied to 5-year time horizon; however, probability of repeat surgery or complications greater in first year post-surgery than subsequent years.

Data Input	Description of Data Source	Comment
Utilities		
Health state utilities	Base case: Arseneau et al. 2006[6] Sensitivity analyses: Punekar et al. 2010,[17] Tsai et al. 2008,[14] Ung et al. 2014,[15] Woehl et al. 2008,[16] GEMINI trial data	Although data from Arseneau et al.[6] or one of the other published articles may provide direct utility values, while utility data captured in the GEMINI-1 study may provide indirect health state values, CDR considered that the data from Arseneau et al. 2006 and the other referenced published articles did not provide direct health state utility values and therefore the applicability of the reported values to the manufacturer's economic model is uncertain. CDR thus considered that despite the limitations, the values from GEMINI-1 would have been more appropriate to inform the base case.
Disutility — serious infection	Calculated based on the inverse of a utility value (0.48) for infection without hospitalization from Brown et al. 2001[7]	Study was in advanced breast cancer. Using the calculation based on inverse of a utility value as a disutility is not appropriate as the population is unlikely to be reflective of UC.
Disutility — tuberculosis	Calculated based on the inverse of a utility value (0.45) for non-fatal tuberculosis from Porco et al. 2006[8]	Uncertain whether data from this population reflect UC patients.
Disutility — malignancy	Calculated based on the inverse of a utility value (0.805) for malignancy (pre-progression) from Hornberger et al. 2008[9]	Study by Hornberger et al. 2008 was in advanced follicular lymphoma; uncertain whether data from this population reflect UC patients.
Disutility — acute hypersensitivity reactions	Disutility value based on pyrexia (fever) from Beusterien et al. 2010[10]	Uncertain whether data from this population reflect UC patients.
Disutility — skin reactions	Disutility value based on skin reactions from reported UK population in Beusterien et al. 2009[11]	Study was undertaken in melanoma patients from UK and Australia. Value used was for UK only. Combined value would be more appropriate; uncertain whether this translates to UC patients.
Resource Use		
CT use	Proportion use of each of the CTs (aminosalicylates, corticosteroids, immunomodulators) was based on interviews with 6 gastroenterologists treating patients with IBD in Canada.	The CDR clinical expert indicated that use of mercaptopurine and olsalazine was overestimated, but generally appropriate.
Health state	Systematic review identified resource use by health state. Numbers of physician consultations, hospitalizations, blood tests, colonoscopies, and surgeries were based on resource	The CDR clinical expert indicated that the number of physician visits was likely overestimated.

Data Input	Description of Data Source	Comment
	use indicated in Tsai et al. 2008[14] and estimates from a single gastroenterologist.	
Adverse Events	AEs selected based on clinical expert opinion: serious infection, tuberculosis, malignancy, acute hypersensitivity reactions, skin reactions. Treatment-related AE rates obtained from relevant clinical trials identified in the manufacturer-submitted NMA.	All patients were assumed to be treated as inpatients (i.e., hospitalized). Potential for double counting given there is already the assumption of hospitalization accounted for within the health states.
Mortality	Considered in a sensitivity analysis. Age and sex specific all-cause mortality sourced from Statistics Canada Survey 3233.	Distribution fitted to modelled population and revised to the 6-weekly and 8-weekly cycles.
Costs		
Drug (biologics)	Vedolizumab: manufacturer Other biologic drugs: Ontario Drug Benefit Exceptional Access formulary (Dec. 2014)	Appropriate
Drug (CT)	Ontario Drug Benefit Formulary (Dec. 2014), Alberta Drug Benefit List (Dec. 2014)	Appropriate
Administration	Drug administration stated to be covered by manufacturer	Appropriate where patient support program is available
Health state (physician consult)	Ontario Schedule of Benefits for Physician Services (May 2014),[28] codes A413 and AE078	CDR clinical expert indicated that the chronic disease billing codes have been removed since the evaluation was submitted. CDR clinical expert also indicated that secondary visits during the year would be billed as partial assessments and there would not be as many as used in the model.
Health state (hospitalization)	Bernstein et al. 2005 (uprated to 2014)[29] Manufacturer-validated value based on CIHI report	The study does not report explicitly which codes were used to identify patients.
Health state (blood tests)	Ontario Schedule of Benefits for Laboratory Services (April 1999)[30] code L393: L372, L396, L397, L399, L417, L418 Other tests added by expert opinion: L348, L329	CDR clinical expert indicated all tests bar L348 were appropriate.
Health state (colonoscopy)	Ontario Schedule of Benefits for Physician Services (May 2014),[28] codes Z494 + 5 anesthesiologist units + E740 + E741 + E747 + E705 + E717 + A120	Appropriate.
Health state (surgery)	Bernstein et al. 2005 (uprated to 2014)[29]	The study does not report explicitly which codes were used to identify patients.
AEs	Costs estimated as weighted averages using data from OCCI database[31] and assumption that all patients were treated as	There was no justification of the use of 5 codes selected to represent serious infection. Other potentially relevant serious

Data Input	Description of Data Source	Comment
	inpatients Averages from multiple codes were used for serious infection, acute hypersensitivity reactions and skin reactions	infections based on the reported clinical trial data include cellulitis and appendicitis.

AE = adverse event; CDR = CADTH Common Drug Review; CIHI = Canadian Institute for Health Information; CSR = Clinical Study Report; CT = conventional therapy; IBD = inflammatory bowel disease; NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; UC = ulcerative colitis; vs. = versus.

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
A 5-year time horizon is appropriate to capture all relevant costs and resources for a patient with UC.	The CDR clinical expert indicated that UC is a chronic condition and ideally would involve a lifetime horizon. CDR did not undertake reanalyses to lengthen the time horizon given that limitations with other parameters that bias the results toward vedolizumab would see this bias increased over time.
The appropriate assessment point (induction period) for vedolizumab is at 6 weeks.	The product monograph indicates that patients who show no evidence of therapeutic benefit by week 10 should discontinue therapy, which differs from both the study end point and the submitted model. CDR was not able to test difference at week 10, given limitations with the data.
Different induction periods among the biologic drugs can be compared directly.	Uncertain. As noted by the clinical expert, this will affect the comparability.
The manufacturer assumed Arseneau et al.(2006) provided the most appropriate utility values, as these values were used in the CADTH HTA report on anti TNF alpha for IBD and one other Canadian cost-utility publication.[6,20] Both of these documents were published in 2009.	In the GEMINI clinical trial, the manufacturer collected data in this patient population using the EQ-5D measurement tool. These values were transformed into utilities and presented by the manufacturer as a sensitivity analysis. It is uncertain why these values were not used in the base-case analysis, as these values are potentially more appropriate as they are in the direct population on which the efficacy data are being assessed.
Disutility estimates were based on published literature that were not in the UC population. Inverse utility values for health states were assumed appropriate to be used to estimate disutility. Not all disutility estimates from the published literature were used.	In the absence of evidence in the UC population, disutility estimates in other populations may be considered appropriate, although associated with substantial uncertainty. The use of the inverse of utility state data to inform disutility is not appropriate. Disutility for skin reactions did not include the Australian cohort, which had a greater disutility. As the audience is in Canada and not the UK, the combined disutility value should have been used.
The manufacturer transformed annual[32] and 6-month[33] surgery rates from published literature to 8-weekly rates and applied these constantly within the model structure. The same practice was applied to proportion of surgery failures and successes.	The rate of surgery potentially overestimates the probability of surgery and time spent in post-surgery complications over the model time horizon, resulting in increased costs and reduced health gains with surgery. The probability of repeat surgery and complications would be expected to be greater in the first 12 months after surgery, rather than remaining constant indefinitely.

Assumption	Comment
Costs from the Ontario Ministry of Health Physician[28] and Laboratory[30] Schedules were used to determine consultation, laboratory, and minor procedure (colonoscopy) costs. Resource use was based on expert opinion.	The CDR clinical expert indicated that the number of consultations was substantially overestimated. Ontario no longer offers a premium for chronic disease assessments, and feedback from the CDR clinical expert indicated that this may have a further impact on the frequency with which patients are seen.
The manufacturer funds drug administration for infused products.	Appropriate; the manufacturer indicated that a patient support program is in place.
Costs associated with surgery and hospitalization were based on published literature that reported 2005–2006 hospital-specific costs from Manitoba.	CDR considered costs from the OCCI Cost Analysis Tool[31] may have been more appropriate and provided more recent estimates (2010-2011) and should have been considered. However, as this tool has been decommissioned, reanalyses using revised costs have not been run.
The manufacturer assumed that all patients on a biologic drug would receive half the amount of CT that patients not on a biologic drug would receive. Under the transition probability assumptions, patients on a biologic drug who transition to the moderate-severe health state can remain in that state for a maximum of one year after which they will discontinue due to lack of response and switch to CT.	Patients are only likely to receive less CT if they are in remission or responding to treatment. For the year that patients transition from the moderate to severe health state, they are likely receiving less CT than is common in clinical practice.
The manufacturer assumed that adverse event rates for placebo in the trial are representative for CT in clinical practice.	Patients in the placebo group of the GEMINI-1 trial (used to inform the CT group of the model) were given a sham infusion to maintain blinding. As patients receiving CT would not receive a sham injection, it is highly unlikely that they would have as many skin reactions as were seen in the clinical trial. Revising the incidence of skin reactions for the CT group to the same as for the vedolizumab group has minimal effect on the ICUR.
The manufacturer included adverse event rates and a cost for adverse events, all of which were assumed to be hospitalized.	There is potential for double counting, as hospitalization is covered separately. The costs associated with hospitalization may include those patients who have adverse events. This may overestimate the costs associated with the moderate-severe health state.

CDR = CADTH Common Drug Review; CT = conventional therapy; EQ-5D = EuroQol 5-Dimensions Questionnaire; HTA = health technology assessment; IBD = inflammatory bowel disease; ICUR = incremental cost-utility ratio; OCCI = Ontario Case Costing Initiative; TNF = tumour necrosis factor; UC = ulcerative colitis.

4. Manufacturer's Results

The manufacturer presented results for three populations: mixed (includes both TNF alpha antagonist–naive and TNF alpha antagonist–failure patients, representing the intention-to-treat population of the vedolizumab trial), TNF alpha antagonist–naive, and TNF alpha antagonist–failure, over a five-year time horizon.

Mixed Population

For the mixed population, the manufacturer conducted the base-case analysis for vedolizumab compared with CT based on the GEMINI-1 clinical trial data Table 11.
The manufacturer reported the following:

- Treatment costs were higher for vedolizumab than for CT.
- Non-treatment costs were higher for CT than for vedolizumab.
- Vedolizumab was associated with higher quality-adjusted life-years (QALYs) (2.006) compared with CT (1.627).
- Vedolizumab had an incremental cost-utility ratio (ICUR) of $60,196 versus CT.

TABLE 11: SUMMARY OF THE MANUFACTURER'S BASE-CASE ANALYSIS FOR THE MIXED POPULATION (GEMINI-1)

Parameter	Vedolizumab	CT	Incremental
Drug-related costs	$37,214	$7,663	$29,551
Non-drug-related costs	$26,843	$33,531	–$6,688
Total costs	$64,057	$41,194	$22,863
Life-years	4.424	4.424	0.000
QALYs	2.006	1.627	0.380
ICUR vs. CT	$60,196		

CT = conventional therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.
Source: Manufacturer's Pharmacoeconomic Report, page 61.[13]

The manufacturer also conducted an exploratory analysis where vedolizumab was compared with CT and adalimumab based on the data from the NMA for all treatments, which alters the costs and QALYs of both vedolizumab and CT (Table 12).

TABLE 12: MANUFACTURER'S EXPLORATORY ANALYSIS FOR THE MIXED POPULATION (NETWORK META-ANALYSIS)

Parameter	Vedolizumab	CT	Adalimumab
Drug-related costs	$44,078	$7,699	$35,855
Non-drug-related costs	$23,818	$32,440	$26,283
Total costs	$67,896	$40,140	$62,138
Life-years	4.424	4.424	4.424
QALYs	2.118	1.692	2.039
ICUR vs. CT	$56,051		
ICUR vs. adalimumab	$38,819		

CT = conventional therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.
Source: Manufacturer's Pharmacoeconomic Report, page 65.[13]

TNF Alpha–Naive Population

For the TNF alpha–naive population, the manufacturer conducted analyses for vedolizumab compared with CT based on the GEMINI-1 clinical trial data, and vedolizumab compared with CT and infliximab based on the NMA data (Table 13 and Table 14).

The manufacturer reported the following:

- The ICUR for vedolizumab versus CT was similar based on GEMINI and the NMA; however, the total costs and QALYs were higher when based on the NMA data than when based on the values from the GEMINI study.
- Vedolizumab had an ICUR of between $54,831 and $56,107 versus CT.
- Vedolizumab dominates infliximab.

TABLE 13: SUMMARY OF THE MANUFACTURER'S BASE-CASE ANALYSIS FOR THE TNF ALPHA–NAIVE POPULATION (GEMINI-1)

Parameter	Vedolizumab	CT
Drug-related costs	$40,984	$7,670
Non-drug-related costs	$25,375	$33,340
Total costs	$66,359	$41,009
Life-years	4.424	4.424
QALYs	2.089	1.637
ICUR	$56,107	

CT = conventional therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.
Source: Manufacturer's Pharmacoeconomic Report, page 66.[13]

TABLE 14: SUMMARY OF THE MANUFACTURER'S BASE-CASE ANALYSIS FOR THE TNF ALPHA–NAIVE POPULATION (NMA)

Parameter	Vedolizumab	CT	Infliximab
Drug-related costs	$51,526	$7,746	$49,337
Non-drug-related costs	$20,189	$30,741	$25,101
Total costs	$71,715	$38,487	$74,439
Life-years	4.424	4.424	4.424
QALYs	2.409	1.803	2.154
ICUR vs. CT	$54,831		
ICUR vs. infliximab	Dominant		

CT = conventional therapy; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; vs. = versus.
Source: Manufacturer's Pharmacoeconomic Report, page 67.[13]

The manufacturer also conducted an exploratory analysis where vedolizumab was compared with adalimumab and golimumab based on the NMA data for all treatments (Table 15).

TABLE 15: MANUFACTURER'S EXPLORATORY ANALYSIS FOR THE TNF ALPHA–NAIVE POPULATION (NETWORK META-ANALYSIS)

Parameter	Vedolizumab	Adalimumab	Golimumab
Drug-related costs	$51,526	$37,978	$34,386
Non-drug-related costs	$20,189	$23,993	$24,610
Total costs	$71,715	$61,971	$58,997
Life-years	4.424	4.424	4.424
QALYs	2.409	2.189	2.157
ICUR vs. adalimumab	$44,266		
ICUR vs. golimumab	$50,355		

ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; vs. = versus.
Source: Manufacturer's Pharmacoeconomic Report, page 79.[13]

TNF Alpha–Failure Population

For the TNF alpha–failure population, the manufacturer conducted analyses for vedolizumab compared with CT based on the GEMINI-1 clinical trial data (Table 16).

The manufacturer reported that vedolizumab had an ICUR of $65,607 versus CT.

TABLE 16: SUMMARY OF THE MANUFACTURER'S BASE-CASE ANALYSIS FOR THE TNF ALPHA–FAILURE POPULATION (GEMINI-1)

Parameter	Vedolizumab	CT
Drug-related costs	$32,659	$7,639
Non-drug-related costs	$28,906	$34,204
Total costs	$61,566	$41,842
Life-years	4.424	4.424
QALYs	1.888	1.587
ICUR	$65,607	

CT = conventional therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TNF = tumour necrosis factor.
Source: Manufacturer's Pharmacoeconomic Report, page 82.[13]

The manufacturer also conducted an exploratory analysis where vedolizumab was compared with CT and adalimumab based on the NMA data for all treatments (Table 17). The exploratory analysis reporting results from the NMA for vedolizumab versus CT differs substantially from the direct evidence from the GEMINI-1 study.

TABLE 17: MANUFACTURER'S EXPLORATORY ANALYSIS FOR THE TNF ALPHA–FAILURE POPULATION (NETWORK META-ANALYSIS)

Parameter	Vedolizumab	CT	Adalimumab
Drug-related costs	$38,020	$7,659	$24,365
Non-drug-related costs	$26,495	$33,584	$30,642
Total costs	$64,516	$41,243	$55,007
Life-years	4.424	4.424	4.424
QALYs	2.033	1.625	1.777
ICUR vs. CT	$57,101		
ICUR vs. adalimumab	$37,189		

CT = conventional therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TNF = tumour necrosis factor; vs. = versus.
Source: Manufacturer's Pharmacoeconomic Report, page 86.[13]

5. CADTH Common Drug Review Reanalysis

CDR undertook reanalyses to the manufacturer's base-case analysis based on the previously identified limitations, where possible. The following reanalyses were undertaken individually and then combined to form the CDR reanalysis base case:

a. **Uncertainty regarding appropriate utility values.** The manufacturer reported the base-case analysis using utility values from the published literature.[6] However, in the GEMINI-1 clinical trial, the manufacturer collected data in this patient population using the EuroQol 5-Dimensions Questionnaire (EQ-5D) measurement tool. These values were transformed into utilities and presented by the manufacturer as a sensitivity analysis. The manufacturer provided clarification at a later date that the values from Arseneau et al. were more appropriate, as the inputs were directly derived from one major source (with the exception of the mild health state), aligned with values reported in the literature, and had been used in past CADTH reports. The manufacturer also cited that utilities for some health states for the CDR pharmacoeconomic review of golimumab[34] were informed by published literature (referring to Arseneau et al.). The manufacturer further noted that Arseneau et al.[6] used direct trial utility data, while incorporation of the GEMINI-1 trial utility values constituted indirect health state values. CDR notes that the direct health state values from Arseneau et al. do not match the health states used in the manufacturer's submission and thus it is reasonable to question their applicability. CDR considered that using more conservative utility estimates was appropriate to highlight the sensitivity of the model to the utility values used. Using the utility values provided by the manufacturer based on the GEMINI-1 clinical trial, the ICUR for vedolizumab versus CT more than doubles, to approximately $132,000.

b. **Inappropriate methods to derive disutility estimates.** The manufacturer used disutility estimates based on published literature that were not in the ulcerative colitis population and applied inverse utility values for health states to estimate disutility, which is not appropriate. CDR undertook reanalyses excluding disutility values; however, the change from the manufacturer base case is negligible.

c. **Surgery rate assumptions.** The use of a constant surgery rate transformed from published literature potentially overestimates the probability of surgery and time spent in post-surgery complications over the model's time horizon, resulting in increased costs and reduced health gains with surgery. The probability of repeat surgery and complications would be expected to be greater in the first 12 months after surgery rather than remaining constant indefinitely. The manufacturer's model did

not allow for variable surgery transitions over time; therefore CDR halved the surgery rates. This had only slight impact, resulting in an ICUR of approximately $61,000 for vedolizumab versus CT.

d. **Physician costs and resource use.** There is uncertainty regarding costs and resource use estimated for each of the health states. Ontario no longer offers a premium for chronic disease assessments, which the CDR clinical expert indicated may have an impact on the frequency with which patients are seen. The CDR clinical expert also indicated that the assumptions overestimated the number of physician visits per patient. CDR reduced the number of annual physician visits to one for patients in remission and those with mild disease, and to two for patients with moderate to severe disease, resulting in an ICUR of approximately $61,000 for vedolizumab versus CT.

e. **CT costs.** There is uncertainty regarding costs and utilization for conventional therapy. The assumption that all patients on a biologic drug would receive half the amount of CT that patients not on a biologic drug would receive is not appropriate. Patients are only likely to receive less CT if they are in remission or responding to treatment. Under the transition probability assumptions, patients on a biologic drug who transition to the moderate to severe health state can remain in that state for a maximum of one year, after which they will discontinue due to lack of response and switch to CT. For this one year, patients are likely to be receiving less CT than is common in clinical practice. Therefore, CDR undertook a reanalysis whereby patients on vedolizumab received the same amount of CT as patients who did not receive vedolizumab. Revising the administration cost resulted in an ICUR of approximately $63,000 for vedolizumab versus CT.

f. **Appropriateness of adverse event rates for CT.** Patients in the placebo group of the GEMINI-1 trial (used to inform the CT group of the model) were given a sham infusion to maintain blinding. As patients receiving CT would not receive a sham injection, it is highly unlikely that they would have as many skin reactions as were seen in the clinical trial. Revising the incidence of skin reactions for the CT group to the same as vedolizumab has minimal effect on the ICUR.

TABLE 18: CADTH COMMON DRUG REVIEW ANALYSIS BASE CASE: VEDOLIZUMAB VERSUS CONVENTIONAL THERAPY

	Scenario	Incremental QALYs	Incremental Costs	ICUR VED vs. CT
0	**Manufacturer's base case**	**0.380**	**$22,863**	**$60,196**
1	Revised utility values (GEMINI-1 trial)	0.165	$22,863	$138,280
2	Exclude disutility values	0.380	$22,863	$60,181
3	Revised surgery rates	0.379	$23,104	$60,967
4	Revised physician cost and resource use	0.380	$23,160	$60,976
5	Same CT costs for biologic drug as for no biologic drug	0.380	$24,024	$63,251
6	Reduced adverse events of CT (skin reactions same for both)	0.380	$22,999	$60,562
7 (1-6)	**Combined reanalysis**	**0.165**	**$24,663**	**$149,581**

CT = conventional therapy; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; VED = vedolizumab; vs. = versus.

The manufacturer's approach to the transition probabilities in the model is unconventional in that the manufacturer indicated that the transition probabilities for the maintenance phase were "optimized" based on a "starting solution" that was not appropriately justified in the submission. The optimization (calibration) process was undertaken using Microsoft Excel Solver based on data from the GEMINI-1 clinical trial and the manufacturer's NMA. In response to a request from CDR, the manufacturer provided data on the proportion of patients moving between the identified health states (remission, mild disease, moderate to severe disease, surgery) from baseline to end of induction and from the start to the end of the maintenance phase from the GEMINI-1,[19] as well as further text on the optimization procedures. CDR identified uncertainty between the actual transitions from the GEMINI-1 clinical trial but determined that the use of the actual transition probabilities from the trial lead to incongruent results. Thus, CDR will not report any reanalyses based on the transition probabilities but notes that the model is sensitive to changes in transition probabilities between the remission, mild, and moderate health states.

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