

CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

VEDOLIZUMAB (Entyvio — Takeda Canada Inc.) Indication: Ulcerative Colitis

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that vedolizumab be listed for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab, a tumour necrosis factor (TNF) alpha antagonist, if the following clinical criterion and condition are met:

Clinical criterion:

- Treatment with vedolizumab should be discontinued if a clinical response is not achieved within six weeks (i.e., a decrease from baseline in partial Mayo score of $\geq 25\%$ and ≥ 2 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1).

Condition:

- Reduction in price to improve the cost-effectiveness of vedolizumab to a level acceptable to the drug plans.

Reasons for the Recommendation:

1. One randomized controlled trial (RCT) (GEMINI-1) demonstrated that treatment with vedolizumab was statistically superior to placebo for achieving clinical response at six weeks (induction) and clinical remission at 52 weeks (maintenance). In addition, treatment with vedolizumab resulted in a greater proportion of patients with mucosal healing and was associated with improvements in quality of life.
2. GEMINI-1 enrolled only patients who had failed previous treatment with conventional therapy or infliximab; patients had not been treated with any other biologic drugs approved for use in the treatment of UC.
3. Despite limitations, two indirect comparisons suggested that vedolizumab is similar to golimumab, infliximab, and adalimumab for inducing clinical response in patients with UC.
4. At the submitted price (\$3,290 per 300 mg vial) and the recommended dosing (300 mg every eight weeks), the CADTH Common Drug Review (CDR) estimated the incremental cost-effectiveness ratio for vedolizumab compared to conventional therapy to range from \$60,000

to \$150,000 per QALY for the treatment of UC in patients who were intolerant to, or had inadequate response to, either conventional therapy or infliximab. However, several limitations could not be addressed in reanalyses which increase the uncertainty of the estimated range.

Background:

Vedolizumab is an immunoglobulin G (IgG1) monoclonal antibody that binds to alpha4beta7 integrin. Vedolizumab is indicated for the 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. It is available in single-use vials containing 300 mg of vedolizumab. The recommended dosing regimen is 300 mg administered by intravenous infusion at initiation, two weeks, six weeks, and then every eight weeks.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of vedolizumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with inflammatory bowel diseases.

Patient Input Information

The following is a summary of information provided by two patient groups that responded to the CDR call for patient input:

- Inflammatory bowel disease can have profound effects on a patient's physical, emotional, and social well-being. Patients often experience debilitating symptoms, including bloody diarrhea, bloating, abdominal pain, fatigue, and a lack of control over bowel movements. They may require frequent and urgent use of a bathroom, with some patients experiencing up to 20 bowel movements in a single day. These symptoms can significantly limit their ability to participate in the activities of daily living, including work and school.
- Patients may experience fear, anxiety, and stress due to the uncertainty of where and when they may experience an urgent bowel movement or a disease flare. Respondents indicated that sustained remission/treatment response is more important than relieving any one symptom.
- The patient groups indicated that a majority of patients would rather receive a biologic drug, despite its potential risks and side effects, than undergo a colectomy. Patients cited the risk of surgical complications and the persistence of extraintestinal manifestations of UC as the primary reasons for preferring non-surgical treatment options.
- Patient groups indicated that individuals with UC have seen remarkable results from biologic drugs when other treatments have failed; however, not everyone responds to the currently available treatments, so more options are essential.

Clinical Trials

The CDR systematic review included one manufacturer-sponsored, double-blind, placebo-controlled RCT (GEMINI-1). The study was 52 weeks in duration and consisted of an induction phase (end points evaluated at six weeks) followed by a maintenance phase (end points evaluated at 52 weeks). The study involved two cohorts of patients who received vedolizumab 300 mg at day 1 and 15:

- Cohort 1: 374 patients participated in the induction phase and were randomized (3:2) to receive either vedolizumab 300 mg or placebo.
- Cohort 2: 521 patients were treated with open-label vedolizumab 300 mg.

For the maintenance phase, patients from cohorts 1 and 2 who were treated with vedolizumab and had achieved a clinical response at week six (n = 373 patients) were randomized (1:1:1) to one of the following regimens: vedolizumab 300 mg every eight weeks, vedolizumab 300 mg every four weeks, or placebo every four weeks. In accordance with the dosage regimen recommended in the product monograph, the CDR review and CDEC deliberations focused on vedolizumab administered every eight weeks.

Patients in GEMINI-1 were required to have failed at least one conventional therapy including corticosteroids, immunomodulators, and/or infliximab. Approximately 45% of enrolled patients had previously used a TNF alpha antagonist (i.e., infliximab). Approximately 38% of patients were taking corticosteroids and 15% of patients were taking immunosuppressants at baseline.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Clinical response — defined as a decrease from baseline in complete Mayo score of $\geq 30\%$ and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. The Mayo score is calculated as the sum of the four subscores of stool frequency, rectal bleeding, physician's global assessment, and the findings of endoscopy. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severely active disease.
- Clinical remission — defined as a Mayo score ≤ 2 points, with no individual subscore > 1 .
- Durable clinical response or remission — defined as achieving clinical response or clinical remission at both weeks 6 and 52.
- Disease worsening — an increase in partial Mayo score of ≥ 3 points from the week six value on two consecutive visits (or an increase to 9 points on two consecutive visits if the week six value is > 6) and a partial Mayo score ≥ 5 points.
- Mucosal healing — defined as a Mayo endoscopic subscore of ≤ 1 .
- Short Form (36) Health Survey (SF-36) — a generic instrument used to assess health-related quality of life. An increase in SF-36 score indicates an improvement in health-related quality of life, and a decrease in score indicates deterioration of health-related quality of life. The physical component score (PCS) reflects the physical function, role-physical, general health, and pain domains, and the mental component score (MCS) reflects the mental health, role-emotional, social functioning, and vitality domains. The minimal clinically important difference (MCID) for the PCS and the MCS is 2.5 to 5 points.
- Inflammatory Bowel Disease Questionnaire (IBDQ) — a 32-item questionnaire used to evaluate how the participant felt during the two weeks before the measurement time point. An increase in IBDQ score indicates an improvement in health-related quality of life. The MCID for the IBDQ is considered to be ≥ 16 points.
- EuroQol 5-Dimensions Questionnaire (EQ-5D) — a generic, preference-based index measure of health-related quality of life. The EQ-5D consists of five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The EQ-5D also contains

a Visual Analogue Scale (VAS) used to record the participant's assessment of his or her health along a vertical 20 cm line, which has health state scores between 0 and 100.

- Treatment failure — defined as patients with any of the following: disease worsening, need for rescue medications or surgical intervention for the treatment of UC, or a study drug-related adverse event leading to discontinuation from the study.

The primary outcomes of GEMINI-1 were clinical response at six weeks (induction phase) and clinical remission at 52 weeks (maintenance phase).

Efficacy

- A statistically significantly greater proportion of vedolizumab-treated patients achieved clinical remission compared with placebo-treated patients in both the induction phase (17% versus 5%) and maintenance phase (42% versus 16%). Similarly, the proportion of patients who achieved durable clinical remission was statistically significantly greater in the vedolizumab group compared with the placebo group. The differences in proportions were:
 - Induction phase: 11.5% (95% confidence interval [CI], 4.7 to 18.3); $P = 0.0009$
 - Maintenance phase: 26.1% (95% CI, 14.9 to 37.2); $P < 0.0001$
 - Durable remission: 11.8% (95% CI, 3.1 to 20.5); $P = 0.008$.
- Of the patients who were taking glucocorticoids at baseline, a statistically significantly greater proportion of vedolizumab-treated patients (22/70; 32%) achieved glucocorticoid-free remission compared with placebo (10/72; 14%). Similar results were reported for the proportion of patients who achieved corticosteroid-free remission and who were also corticosteroid-free for 180 days prior to week 52 (29% versus 11%). The differences in proportions were:
 - Glucocorticoid-free remission: 17.6% (95% CI, 3.9 to 31.3); $P = 0.01$
 - Corticosteroid-free remission: 17.5% (95% CI, 4.5 to 30.5); $P = 0.008$.
- A statistically significantly greater proportion of vedolizumab-treated patients achieved clinical response and durable clinical response compared with placebo-treated patients (47% versus 26% and 42% versus 16%, respectively). The differences in proportions were:
 - Induction phase: 21.7% (95% CI, 11.6 to 31.7); $P < 0.0001$
 - Durable clinical response: 32.8% (95% CI, 20.8 to 44.7); $P < 0.0001$.
- The difference in mean change from baseline in IBDQ was statistically significantly greater in the vedolizumab group compared with the placebo group at six weeks (18.0; 95% CI, 11.0 to 24.9) and 52 weeks (26.1; 95% CI, 15.2 to 36.9).
- The differences in mean change from baseline for the SF-36 PCS and MCS were statistically significantly greater in the vedolizumab group compared with the placebo group:
 - SF-36 PCS: 2.7 (95% CI, 1.3 to 4.1) at week 6 and 4.7 (95% CI, 2.3 to 7.2) at week 52
 - SF-36 MCS: 4.4 (95% CI, 2.5 to 6.4) at week 6 and 6.6 (95% CI, 3.4 to 9.8) at week 52.
- Changes from baseline for the EQ-5D and EQ-5D VAS were statistically significantly greater for vedolizumab compared with placebo at week 6 and 52. The differences in mean change from baseline were:
 - EQ-5D: -0.5 (95% CI, -0.7 to -0.2) at week 6 and -0.6 (95% CI, -1.1 to -0.1) at week 52
 - EQ-5D VAS: 9.6 (95% CI, 5.8 to 13.5) at week 6 and 12.5 (95% CI, 6.7 to 18.4) at week 52.
- When the definition for mucosal healing was a Mayo endoscopic subscore ≤ 1 , a statistically significantly greater proportion of vedolizumab-treated patients demonstrated mucosal healing compared with placebo in both the induction and maintenance phases. When a more restrictive definition of mucosal healing is used (i.e., Mayo endoscopic subscore of 0),

there was no statistically significant difference between vedolizumab and placebo ($P = 0.69$) in the induction phase. However, there was a statistically significant difference favouring vedolizumab in the maintenance phase ($P < 0.001$). The differences in proportions for achieving mucosal healing were:

- Mayo endoscopic subscore ≤ 1 : 16.1% (95% CI, 6.4 to 25.9) at week 6 and 32.0% (95% CI, 20.3 to 43.8) at week 52
- Mayo endoscopic subscore = 0: 0.9% (95% CI, -3.4 to 5.2) at week 6 and 20.1% (95% CI, 10.6 to 29.6) at week 52.

Harms (Safety and Tolerability)

- At least one serious adverse event was reported for 8% of vedolizumab-treated patients and 16% of placebo-treated patients. UC was the most commonly reported serious adverse event, occurring in 2% of the vedolizumab group and 6% of the placebo group.
- At least one adverse event was reported for 82% of vedolizumab-treated patients and 84% of placebo-treated patients. The most commonly reported adverse events in patients treated with vedolizumab were headache (13%), nasopharyngitis (13%), arthralgia (9%), upper respiratory tract infection (8%), cough (6%), abdominal pain (6%), nausea (6%), anemia (6%), fatigue (5%), and influenza (5%).
- Withdrawals due to adverse events were reported for 6% of patients treated with vedolizumab and 12% of patients treated with placebo. The most commonly cited reason was UC (4% with vedolizumab and 8% with placebo).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing vedolizumab with standard of care: conventional therapy (i.e., aminosalicylates, corticosteroids, and immunomodulators) or TNF alpha antagonist therapy. The primary analysis was on a mixed population consisting of patients who were either experienced or naive to TNF alpha antagonists; however, subgroup analyses were also reported. The manufacturer used a decision-tree framework to represent the induction phase (six weeks), followed by a cohort health state transition Markov model structure to capture maintenance treatment over a five-year time horizon (with eight-week cycles), from the perspective of the public health care payer. The model is driven by transition probabilities that were based on data from the GEMINI-1 trial (for vedolizumab and conventional therapy) and a network meta-analysis (NMA) (for the other biologic drugs). Health state utility values were based on a single published article, although other utility values were tested in sensitivity analyses. Disutility values for adverse events were based on published literature. Costs for drug acquisition are based on information from the manufacturer as well as the Ontario Drug Benefit Formulary, while drug administration costs and resource use (i.e., physician visits, hospitalization, lab tests, and surgery) were reflective of health states and derived from Canadian data sources. The manufacturer reported an incremental cost-utility ratio (ICUR) of \$60,196 per quality-adjusted life-year (QALY) for vedolizumab compared with conventional therapy in the mixed population.

CDR identified the following limitations with the manufacturer's pharmacoeconomic model:

- Uncertainty regarding appropriate utility values
- Inappropriate methods to derive disutility estimates
- Assumption of a constant surgery rate potentially overestimates probability of surgery and time spent in post-surgery complications over the model time frame
- Uncertain health state costs and resource use

- Possible underestimation of conventional therapy use in patients receiving vedolizumab
- Overestimation of adverse event rates for conventional therapy
- Concerns with the NMA as identified by CDR limits information on cost-effectiveness compared with other biologic drugs
- Uncertainty regarding the calculation of transition probabilities for the maintenance phase
- Differences in assessment point for vedolizumab in the clinical trials and economic model (assessment at 6 weeks) compared to that recommended in the Health Canada product monograph (assessment at 10 weeks).
- Five-year time horizon short for a chronic condition.

CDR tested the limitations regarding utility values, surgery and adverse event rates, costs, and resource use resulting in an ICUR ranging from \$60,000 (manufacturer's base case) to \$150,000 per QALY (CDR revised base case) for vedolizumab compared with conventional therapy. Based on the revised base case, a price reduction of greater than 50% would be required to lower the ICUR to a conventionally accepted threshold; however, CDR was unable to test the uncertainty associated with other identified limitations.

At the submitted price of \$3,290 per 300 mg vial and the recommended dosing (300 mg every eight weeks), the cost of vedolizumab in the first year (\$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).

Other Discussion Points:

CDEC noted the following:

- Two indirect comparisons suggested that vedolizumab has similar efficacy for inducing clinical response compared with golimumab, infliximab, and adalimumab. Given the heterogeneity across the studies, there is uncertainty regarding the comparative efficacy of these drugs for maintaining clinical remission.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- The product monograph states that there are no data from clinical trials for the use of vedolizumab in patients previously treated with biologic drugs other than infliximab.
- There are no direct comparisons of vedolizumab against other treatments approved for use in the treatment of UC.
- The long-term efficacy and safety profile of vedolizumab requires further evaluation.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

Regrets:

July 15, 2015: None

October 20, 2015: One CDEC member was unable to attend this portion of the meeting.

Conflicts of Interest:

July 15, 2015: None

October 20, 2015: None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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