CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

VEDOLIZUMAB
(Entyvio — Takeda Canada Inc.)
Indication: Crohn's Disease

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that vedolizumab be reimbursed for the treatment of adults with moderately to severely active Crohn's disease (CD) if the following criterion and conditions are met:

Criterion:
Treatment with vedolizumab should be discontinued if a clinical response is not achieved prior to the administration of a fourth dose of vedolizumab.

Conditions:
1. The cost of treatment with vedolizumab should not exceed the drug plan cost of the least costly alternative biologic treatment option.
2. Patients treated with vedolizumab should be under the care of a specialist physician with experience in the diagnosis and management of CD.

Of Note:
A clinical response is defined as an improvement in Crohn's Disease Activity Index (CDAI) score of at least 70 points.

Reasons for the Recommendation:
1. Three phase 3, placebo-controlled double-blind randomized controlled trials (RCTs) investigated the effects of vedolizumab on treatment induction (GEMINI II and GEMINI III) or maintenance (GEMINI II) in patients with moderate to severe CD. Patients who received vedolizumab were more likely to achieve clinical remission at six weeks than those who were treated with placebo in both GEMINI II and GEMINI III. The proportion of vedolizumab-treated patients who achieved clinical remission was greater at 10 weeks compared with that at six weeks in GEMINI III.
2. A greater proportion of the subpopulation of patients who had previously failed treatment with at least one tumour necrosis factor (TNF) alpha antagonist achieved clinical remission compared with placebo at 10 weeks in GEMINI III.

3. There is insufficient evidence to suggest that there is a meaningful clinical difference between vedolizumab and other biologic drugs. Although five indirect comparisons reviewed by the CADTH Common Drug Review (CDR) included comparisons of vedolizumab against other biologic treatments for CD, limitations associated with these comparisons precluded any definitive conclusions regarding the comparative efficacy and safety of vedolizumab compared with TNF alpha antagonists.
4. At the submitted price of $3,290 per 20 mL vial, vedolizumab is more costly than adalimumab and the infliximab subsequent entry biologic (SEB), Inflectra. There was insufficient information available to assess the cost-effectiveness of vedolizumab in the subpopulation of patients with moderate to severe CD who have not responded previously to treatment with one or more TNF alpha antagonists.

Background:
Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to alpha4 beta7 integrin to inhibit leukocyte migration into the gut mucosa. Vedolizumab is indicated for use in the treatment of adults with ulcerative colitis and CD. This CDR submission is for the treatment of adults with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or who have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids.

Vedolizumab is available in single-use vials containing 300 mg vedolizumab. It is administered via intravenous (IV) infusion and must be reconstituted and diluted prior to administration. For the treatment of CD, the product monograph recommends a dosage of 300 mg IV at initiation (i.e., week 0), two weeks, six weeks, and every eight weeks thereafter. The product monograph states that therapy with vedolizumab should be discontinued for patients who fail to show evidence of therapeutic benefit by 14 weeks.

Summary of CDEC Considerations
CDEC considered the following information prepared by CDR: a systematic review of RCTs of vedolizumab in the treatment of CD, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals living with CD.

Patient Input Information
Two patient groups responded to the CDR call for patient input (the Gastrointestinal Society and Crohn's and Colitis Canada). Information was collected through discussions and interviews with patients, caregivers, and gastroenterologists; surveys and questionnaires; and a review of published reports and information. CDEC heard the following:

- CD 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.
- Patients may experience fear, anxiety, and stress due to the uncertainty regarding where and when they may experience an urgent bowel movement or a disease flare. These symptoms can significantly limit their ability to participate in the activities of daily living, including work and school.

- Patient groups indicated that individuals with CD found biologic drugs worked well when other treatments have failed; however, not everyone responds to the currently available treatments, so more options are needed.
- Patient groups expressed an understanding of the potential risks associated with biologic treatments and noted that those living with CD are often willing to accept these risks rather than undergo surgery, which they consider to be a last resort.

Clinical Trials

The CDR systematic review included two pivotal, multi-centre, double-blind RCTs (GEMINI II and GEMINI III). Both studies enrolled adults with moderate to severe active CD who failed treatment with one or more TNF alpha antagonists, immunomodulators, and/or corticosteroids. The GEMINI II study included a six-week induction phase followed by a 48-week maintenance phase (i.e., total treatment duration of 52 weeks). The six-week induction phase of GEMINI II enrolled a total of 1,115 patients in the following two cohorts: A double-blind cohort, who were randomized (3:2) to receive vedolizumab or placebo (n = 368); and an open-label cohort, who were treated with open-label vedolizumab (n = 748) and were not included in the induction analysis set. Patients in the double-blind cohort were scheduled to receive either 300 mg vedolizumab or placebo at weeks 0 and 2 (i.e., a total of two infusions). Those in the open-label cohort received unmasked 300 mg vedolizumab at weeks 0 and 2. In the maintenance phase of GEMINI II, patients from both the double-blind and open-label cohorts of the induction phase who received vedolizumab in the induction phase and who demonstrated a clinical response (CDAI score at least 70 points lower than baseline) at six weeks were randomized (1:1:1) to double-blind treatment with vedolizumab every four weeks, vedolizumab every eight weeks, or placebo. The maintenance phase began at the week 6 visit and concluded after 52 weeks.

GEMINI III was a phase 3, multinational, randomized, double-blind, placebo-controlled study (N = 416). The study was designed such that 75% of the study population was to have failed previous treatment with at least one TNF alpha antagonist and 25% were to have been naive to TNF alpha antagonist therapy. Patients were randomized (1:1) to receive either vedolizumab or placebo at weeks 0, 2, and 6 (i.e., a total of three infusions).

Outcomes

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

- Clinical remission (CDAI score ≤ 150)
- Durable clinical remission (CDAI score ≤ 150 points at 80% or more of study visits during the maintenance phase)
- Corticosteroid-free clinical remission
- Enhanced clinical response (CDAI score at least 100 points lower than baseline)
- Short Form (36) Health Survey (SF-36)
- Inflammatory Bowel Disease Questionnaire (IBDQ)
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Clinical remission at six weeks and enhanced clinical response (CDAI score at least 100 points lower than baseline) at six weeks were the co-primary end points of the induction phase of GEMINI II. Clinical remission in the overall study population at 52 weeks was the primary end

point of the maintenance phase of GEMINI II. Clinical remission at six weeks in the TNF alpha–failure subpopulation was the primary end point in GEMINI III.

Efficacy

Induction Treatment

After six weeks, vedolizumab-treated patients (15.0% to 19.1%) were more likely to achieve clinical remission during the six-week induction phase than those treated with placebo (7% to 12.1%) in both GEMINI II and GEMINI III (risk differences [RD] were 7.8% [95% confidence interval (CI), 1.2 to 14.3] in GEMINI II and 6.9% [95% CI, 0.1 to 13.8] in GEMINI-III). The proportion of vedolizumab-treated patients with clinical remission further increased at the week 10 evaluation compared with placebo (28.7% versus 13.0%; RD 15.5% [95% CI, 7.8 to 23.3]).

In the TNF alpha–failure subpopulation, there was no statistically significant difference between vedolizumab and placebo for clinical remission (RD 6.2% [95% CI, −9.2 to 21.3] in GEMINI II and RD 3.0% [95% CI, −4.5 to 10.5] in GEMINI III) at week 6. This was the primary end point of GEMINI III; therefore, failure to demonstrate a statistically significant difference between vedolizumab and placebo stopped the statistical testing hierarchy at this end point. The proportion of vedolizumab patients with clinical remission increased at the 10-week evaluation compared with placebo (26.6% versus 12.1%; RD 14.4% [95% CI, 5.7 to 23.1]).

There was no statistically significant difference between vedolizumab and placebo for the proportion of patients with enhanced clinical response at six weeks in GEMINI II (RD 5.7% [95% CI, −3.6 to 15.0]); $P = 0.2322$); however, there was a greater proportion of vedolizumab-treated patients with enhanced clinical response compared with placebo at both week 6 and week 10 in GEMINI III (RD 16.4% [95% CI, 7.7 to 25.2] and 23.7 [95% CI, 14.5 to 32.9], respectively). Results in the TNF alpha–failure subgroup analyses were similar to the overall populations in both studies.

Vedolizumab-treated patients demonstrated greater improvements from baseline in IBDQ in both GEMINI II and GEMINI III. Statistical analyses were not conducted; mean differences for vedolizumab versus placebo were 6.5 (95% CI, −0.5 to 13.6) in GEMINI II and 9.1 (95% CI, 3.1 to 15.1) in GEMINI III at six weeks and 13.6 (95% CI, 7.3 to 19.9) in GEMINI III at 10 weeks.

For the SF-36, the estimated treatment differences favour vedolizumab; however, the lower bound of the 95% CI includes or crosses 0 for all of the evaluations at six weeks. Mean EQ-5D scores improved in both the vedolizumab and placebo groups in the induction phase. The estimated treatment differences for the EQ-5D score favoured vedolizumab; however, the lower bound of the 95% CI excludes only 0 in the evaluation at 10 weeks in the GEMINI III trial. Vedolizumab was associated with greater improvements in EQ-5D VAS scores at both week 6 and week 10; however, the improvements were similar between the two treatment groups in GEMINI II.

Maintenance Treatment

There was a statistically significantly greater proportion of vedolizumab-treated patients who demonstrated clinical remission at 52 weeks compared with the placebo-treated patients (39.0% versus 21.6%; RD 17.4% [95% CI, 7.3 to 27.5]; $P = 0.0007$). The proportion of patients achieving clinical remission was reduced in the TNF alpha-failure subgroup (28.0% with

vedolizumab and 12.8% with placebo); however, the RD between the two groups was similar to the analysis using the overall treatment population (15.2 [95% CI, 3.0 to 27.5]).
There was no statistically significant difference between the vedolizumab and placebo groups for the proportion of patients who achieved durable clinical remission (21.4% versus 14.4%; RD 7.2 [95% CI, −1.5 to 16.0]; *P* = 0.1036).

A statistically significantly greater proportion of vedolizumab-treated patients demonstrated enhanced clinical response at 52 weeks compared with placebo-treated patients (43.5% versus 30.1%; RD 13.4% [95% CI, 2.8 to 24.0]; *P* = 0.0132). The proportion of patients achieving enhanced clinical response was reduced in the TNF alpha-failure subgroup (8.8% [95% CI, −4.6 to 22.1]).

At the beginning of the maintenance phase, corticosteroids were being used by 53% of patients in the vedolizumab group and 54% of patients in the placebo group. After 52 weeks, a statistically significantly greater proportion of vedolizumab-treated patients achieved corticosteroid-free clinical remission compared with the placebo group (31.7% versus 15.9%; RD 15.9% [95% CI, 3.0 to 28.7]; *P* = 0.0154). In the TNF alpha-failure subgroup analysis, 24.4% of vedolizumab-treated patients achieved corticosteroid-free remission compared with no placebo-treated patients (RD 24.4 [95% CI, 2.4 to 45.1]).

Treatment with vedolizumab was associated with a greater improvement in IBDQ score compared with placebo (mean difference 15.1 [95% CI, 4.4 to 25.9]). The SF-36 physical component summary (PCS) and mental component summary (MCS) showed improvement from baseline in both the vedolizumab and placebo groups. The mean differences between vedolizumab and placebo were 3.5 (95% CI, 1.1 to 5.9) for the SF-36 PCS and 3.0 (95% CI, −0.3 to 6.2) for the SF-36 MCS. Mean improvements from baseline to week 52 were greater with vedolizumab compared with placebo for both the EQ-5D (−0.5 [95% CI, −0.9 to −0.1]) and the EQ-5D Visual Analogue Scale (VAS) (12.4 [95% CI, 7.0 to 17.8]).

Harms (Safety and Tolerability)
The manufacturer conducted safety analyses for the induction phase and for the combined induction and maintenance phases. Data from the induction phase of GEMINI III were pooled with data from the induction phase of GEMINI II for the manufacturer's induction safety analysis, and data from both phases of GEMINI II were used in the evaluation of safety in the induction/maintenance population.

A similar proportion of patients in the vedolizumab and placebo groups experienced at least one adverse event in the induction population (57% and 60%, respectively) and in the induction/maintenance population (88% versus 84%, respectively). The proportion of patients who experienced at least one serious adverse event was the same in the vedolizumab and placebo groups in the induction population (7% in each group) and slightly greater with vedolizumab in the induction/maintenance population (18% versus 15%, respectively). Withdrawals due to adverse events were more common in the placebo group compared with the vedolizumab group in both the induction (5% versus 3%, respectively) and induction/maintenance populations (10% versus 8%, respectively). For the vedolizumab group, there were no other adverse events leading to discontinuation that were reported for more than one patient.

Cost and Cost-Effectiveness

Vedolizumab is available in 300 mg/20 mL vials for intravenous infusion at the current market price of $3,290 per vial. At the recommended dosing of vedolizumab for CD of 300 mg at zero, two, and six weeks followed by every eight weeks thereafter, the cost of vedolizumab is $26,320 per patient in the first year and an average of $21,458 per patient in subsequent years.

The manufacturer submitted a cost comparison of vedolizumab to branded infliximab (Remicade) and adalimumab in adults with CD. The perspective was that of a public drug payer with a time horizon of two years to incorporate both the induction and maintenance phases of treatment. The assumption of clinical similarity was based on a manufacturer-funded indirect treatment comparison. Only drug costs were considered; all other health care costs were assumed to be equal among comparators. Proportions of patients using standard versus escalated doses of infliximab and adalimumab in the base case, and the approved dose versus a single extra dose of vedolizumab in a sensitivity analysis, were derived from the ACCENT I, CLASSIC II, and GEMINI II trials, respectively.

Key limitations in the manufacturer's analysis included uncertainty regarding the clinical similarity of comparators, the availability of a new and less expensive SEB infliximab, and uncertainty regarding the comparability and relative proportions of patients using escalated dosing for each treatment.

In CDR's reanalysis, in the first year, at the approved dose of vedolizumab and standard doses of the comparators, the cost of branded infliximab ($31,602 per patient) is $5,282 (20%) more than the cost of vedolizumab ($26,320 per patient); adalimumab ($22,211 per patient) is $4,109 (16%) less than vedolizumab; and SEB infliximab ($16,800 per patient) is $9,520 (36%) less than vedolizumab when considering comparator drug costs based on Ontario Drug Benefit Formulary Exceptional Access Program. In subsequent years, at the approved dose of vedolizumab and standard doses of the comparators, the cost of branded infliximab ($25,765 per patient) is $4,306 (20%) more than the cost of vedolizumab ($21,458 per patient); adalimumab ($19,315 per patient) is $2,143 (10%) less than vedolizumab; and SEB infliximab ($13,697 per patient) is $7,762 (36%) less than vedolizumab. The reanalysis is based on the assumptions of clinical similarity among comparators, for which there is considerable uncertainty, and it was not possible for CDR to develop a robust comparative assessment considering escalated dosing.

Other Discussion Points:

There were no studies that directly compared vedolizumab to the TNF alpha antagonists, adalimumab and infliximab, for induction or maintenance treatment of CD. Five indirect comparisons that were reviewed by CDR included comparisons of vedolizumab against other biologic treatments for CD. However, each of these comparisons was limited by substantial heterogeneity associated with the study designs and the characteristics of patients in the studies included in the indirect comparisons, which precluded any definitive conclusions regarding the comparative efficacy and safety of vedolizumab compared with TNF alpha antagonists.

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 Wijeysundera.

September 21, 2016 Meeting

Regrets:

Four CDEC members were unable to attend.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary reimbursement 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.

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