CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

VEDOLIZUMAB (ENTYVIO — TAKEDA CANADA INC.)

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

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that vedolizumab subcutaneous (SC) be reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or infliximab, a tumor necrosis factor alpha (TNFα) antagonist, only if the following conditions are met.

Conditions for Reimbursement

1. Reimburse in a similar manner to the IV formulation of vedolizumab.
2. Therapy with vedolizumab SC should only be commenced in patients who have achieved clinical response after induction therapy with vedolizumab IV 300 mg.
3. The drug plan cost of treatment with vedolizumab solution for SC injection should not exceed the drug plan cost of the least costly biologic currently reimbursed for the treatment of UC.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	1.0
Publication Date:	May 2020
Report Length:	9 Pages

CADTH

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

VEDOLIZUMAB (ENTYVIO — TAKEDA CANADA INC.)

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

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that vedolizumab subcutaneous (SC) be reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or infliximab, a tumour necrosis factor alpha (TNFα) antagonist, only if the following conditions are met.

Conditions for Reimbursement

1. Reimburse in a similar manner to the IV formulation of vedolizumab.
2. Therapy with vedolizumab SC should only be commenced in patients who have achieved clinical response after induction therapy with vedolizumab IV 300 mg.
3. The drug plan cost of treatment with vedolizumab solution for SC injection should not exceed the drug plan cost of the least costly biologic currently reimbursed for the treatment of UC.

Reasons for the Recommendation

1. In the double-blind randomized placebo-controlled trial (VISIBLE 1), more patients in the vedolizumab SC group showed clinical remission at week 52 when compared to the placebo group (46.2% versus 14.3%, respectively; adjusted risk difference [RD] = 32.3%; 95% confidence interval [CI], 19.7% to 45%; P < 0.001). These findings were consistent in both anti-TNF-naive and -experienced populations. VISIBLE 1 was not designed to compare the IV and SC forms of vedolizumab; however, numerically similar rates of clinical remission were seen in both the vedolizumab IV group and the vedolizumab SC group when either group was compared to placebo. More participants allocated to receive vedolizumab SC (as opposed to placebo) achieved a durable clinical response (64.2% versus 28.6%; adjusted RD = 36.1%; 95% CI, 21.2 to 50.9; P < 0.001). Those who received vedolizumab SC had a statistically and clinically significant improvement in health-related quality of life as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) total score using a minimal important difference of greater than 15 points. The change from baseline was 21.47 (standard deviation [SD] = 5.43) points for placebo compared to 65.3 points (SD = 3.94) for vedolizumab SC with a mean difference of 43.87 (SD = 6.71; P < 0.001). In the EuroQol 5-Dimensions (EQ-5D) total index score (using a minimal important difference of greater than 0.05), the change from baseline for placebo was 0.075 (SD = 0.206) compared to 0.141 (SD = 0.201) for vedolizumab SC.
2. A network meta-analysis (NMA) was performed by the sponsor to evaluate [redacted] The applicability of the sponsor-submitted NMA is affected by the lack of transparency in the systematic review, the limited size of the evidence base, the potential limitations in the submitted analysis, and the heterogeneity in the design of the included studies and across populations. Additionally, there was insufficient analysis conducted to account for trial and clinical heterogeneity, thus limiting the utility and the robustness of the results.
3. At the submitted price, vedolizumab SC is not cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year. The annual cost of vedolizumab SC would be $25,501 (including the cost of induction therapy with IV vedolizumab) and $21,385 per patient in the first and subsequent years, respectively. Based on publicly available prices, the annual cost of

infliximab biosimilar, the least costly biologic for this indication, is $15,776 and $13,804 in the first and subsequent years, respectively. Given the uncertainty regarding the comparative effectiveness of vedolizumab with other biologics and the limitations of the cost-utility analysis, there is insufficient evidence to justify a cost premium over the least expensive biologic reimbursed for the treatment of moderate-to-severe UC.

Discussion Points

- The committee noted that although in VISIBLE 1 vedolizumab SC performed similar to vedolizumab IV when compared to placebo, the assessment of the comparison of vedolizumab SC with vedolizumab IV was descriptive in nature and was not formally designed and tested as a noninferiority hypothesis.
- The committee discussed that although subgroup analyses were performed to examine the consistency of the treatment effect observed for the primary and all secondary outcomes, the sample size of the clinical or therapeutic subgroups precluded a proper interpretation of the data as they were considered underpowered to detect a significant effect in such specific populations.
- The committee noted that while it is proposed that the mechanism of action of vedolizumab is targeted at gut lymphocytes, there is no evidence that this mechanism confers any specific advantages in efficacy or safety over other treatments available for UC.

Background

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody that binds exclusively to the alpha 4 beta 7 human integrin on pathogenic gut-homing lymphocytes, acting as a gut-selective anti-inflammatory biologic. The IV formulation has been approved by Health Canada for adults with moderately to severely active Crohn disease and for the treatment of adult patients with moderately to severely active UC who have had an inadequate response or loss of response to, or who were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist. The SC injection formulation of vedolizumab is the current focus of this review. It is meant to be used in the maintenance phase of treatment at 108 mg every two weeks (vial with 108 mg/0.68 mL) after induction with the IV formulation. The Health Canada approved indication of the SC formulation is “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 TNFα antagonist.”

Submission History

Vedolizumab IV has been previously reviewed by CADTH through the Common Drug Review process 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 (on July 15, 2015, the indication was approved to be reimbursed if conditions were met)
- the treatment of adult patients with moderately to severely active Crohn disease (on September 21, 2016, CADTH recommended that vedolizumab should be reimbursed if criteria were met).

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CADTH: a systematic review of clinical trials of vedolizumab SC, a summary and critique of a sponsor-provided indirect treatment comparisons, and a critique of the sponsor’s pharmacoeconomic evaluation. The committee also considered input from a clinical expert(s) with experience in treating patients with UC, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Gastrointestinal Society, provided input for this submission. Patient perspectives were obtained from surveys and interviews. The following is a summary of key input from the perspective of the patient group:

- The group described how UC represents a disabling, life-long gastrointestinal condition that more commonly affects youth and younger working-age individuals in their day-to-day lives, sometimes causing them to experience isolation, anxiety, and debilitating, frequent, and urgent bowel movements that can involve rectal bleeding and anemia. Canada has one of the highest prevalence rates of UC in the world.
- Patients often seek treatment options that can reduce or eliminate their symptoms, and are regularly longing for treatments that could protect their ability to work, attend school and social events, and perform basic day-to-day activities.
- The patient group reported that many current treatments can have undesirable effects due to the need for long-term use and how they require new and effective options to achieve mucosal healing and decrease debilitating symptoms. Therapies that are effective for milder forms of the disease often fail to achieve remission with moderately to severely active UC.
- Patients preferred drugs that are convenient and easy to use.
- Given that all individuals respond differently to therapies, it was considered imperative that patients have a variety of options for treatment.

Clinical Trials

The CADTH systematic review included one double-blind randomized placebo-controlled trial: the VISIBLE 1 study. The trial screened 614 patients, of which 383 (with moderately to severely active UC) were eligible and received an open-label administration of vedolizumab 300 mg IV infusion at weeks 0 and 2. At week 6, patients were assessed for clinical response, defined as a reduction in total Mayo score of three or more points and a decrease of 30% or more from baseline, plus a decrease in rectal bleeding subscore of one or more, or absolute rectal bleeding subscore of one or less. After induction with IV vedolizumab, 216 patients were considered responders and randomized to vedolizumab SC (108 mg vedolizumab SC every two weeks), vedolizumab IV (300 mg every eight weeks), or placebo in a 2:1:1 ratio, with stratification by concomitant corticosteroid use, clinical remission status at week 6, and previous anti-TNF failure or concomitant immunomodulator use. Patients who did not achieve a clinical response at week 6 received a third open-label 300 mg vedolizumab IV dose and were reassessed for clinical response at week 14 (defined as a reduction in partial Mayo score of ≥ 2 points and a decrease of ≥ 25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point, or absolute rectal bleeding subscore of ≤ 1 point). Those achieving a clinical response at week 14 had the option to enrol in the open-label extension study, while those who did not respond at week 14 were discontinued. All patients were then evaluated every eight weeks for a total follow-up of 52 weeks.

The VISIBLE 1 study had a low risk of bias, with an appropriate randomization process, blinding of participants, investigators, and clinicians, and adequate analysis. Adjustment for multiplicity to control for an overall type I error rate and follow-up were adequately performed. The sample size obtained provides enough power for the main and all secondary outcomes, but it was not powered for safety outcomes and subgroup analyses. The VISIBLE 1 study was not designed to provide a formal noninferiority comparison of vedolizumab IV to vedolizumab SC. Attrition was high in the maintenance phase, mainly due to lack of effect of the intervention (especially in the placebo group); this led to large and different rates of missing data across groups, which could bias conclusions toward the null due to a less symptomatic placebo group. Although missing patients were treated as nonresponders, the sensitivity analyses performed for the treatment of missing data generally resulted in consistent conclusions. In terms of external validity, the strict controlled settings of the randomized controlled trial in which patients were evaluated thoroughly and followed-up closely might not be applied in real-life settings, particularly in relation to the SC application of the drug. The extension study (Study SC-3030) could provide more information in terms of the real-life application of the new SC administration of vedolizumab.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, the committee discussed the following:

- clinical remission defined as a total Mayo score of two or less and no individual subscore greater than one at 52 weeks
- endoscopic improvement (e.g., mucosal healing) assessed as Mayo endoscopic subscore of one or less (normal or inactive disease or mild disease) at 52 weeks
- durable clinical response, defined as clinical response at weeks 6 and 52
- durable clinical remission, defined as clinical remission at weeks 6 and 52
- corticosteroid-free remission, defined as patients using oral corticosteroids at baseline (week 0) who have discontinued oral corticosteroids and are in clinical remission at week 52.
- health-related quality of life:
    - EQ-5D score index
    - IBDQ scores
    - Work and Productivity and Activity Impairment Questionnaire: Ulcerative Colitis instrument scores.

For the purpose of this review, these outcomes were assessed for the comparison of vedolizumab SC versus placebo, and any assessment of the comparison of vedolizumab SC with vedolizumab IV is descriptive in nature and not formally designed and tested as a noninferiority hypothesis.

Efficacy

Of 216 patients enrolled in the maintenance phase, 106 were randomized to vedolizumab SC, 54 to vedolizumab IV, and 56 to placebo. More patients in the vedolizumab SC group showed clinical remission at week 52 when compared to placebo (46.2% versus 14.3%, respectively; adjusted RD = 32.3%; 95% CI, 19.7% to 45%; P < 0.001), and these results occurred in both the anti-TNF-naive and -experienced populations. Numerically similar rates of clinical remission were seen in the vedolizumab IV group compared to the placebo group. Vedolizumab SC when compared to placebo also had higher effects in the outcomes of durable clinical response (64.2% versus 28.6%; adjusted RD = 36.1%; 95% CI, 21.2 to 50.9; P < 0.001) and endoscopic improvement and mucosal healing (56.6% versus 21.4%; adjusted RD = 35.7%; 95% CI, 22.1 to 49.3; P < 0.001). Corticosteroid-free remission was not statistically significantly different between vedolizumab SC and placebo (28.9% versus 8.3%; adjusted RD = 20.6%; 95% CI, –4.5 to 43.7). No colectomies were performed or required during the study. Vedolizumab SC had a statistically and clinically significant effect in IBDQ total score and in the EQ-5D total index score. Also, Work Productivity and Activity scores were statistically significantly improved in the vedolizumab SC group versus the placebo group. In all these outcomes, vedolizumab SC performed similar to vedolizumab IV when compared to placebo, although this comparison was not formally tested for noninferiority. Sensitivity analyses support the robustness of results. The trial was not powered for subgroup analyses.

Harms (Safety)

Overall, there were no concerns of harms from the VISIBLE 1 trial and its long-term extension study (Study SC-3030), either for adverse events (AEs) or serious adverse events (SAEs), or harms of special interest. The most common AEs were worsening of UC disease activity, nasopharyngitis, anemia, and upper respiratory tract infections. Two infections in the vedolizumab SC group were considered serious (one anal abscess and one case of peritonitis) but were not deemed treatment-related and did not lead to discontinuation. Injection-site reactions (mainly rash, swelling, erythema, and pruritus) occurred in 11 patients (10.4%) receiving vedolizumab SC, one patient (1.9%) receiving vedolizumab IV (plus matching SC placebo), and no patients receiving placebo. No deaths or major adverse cardiac events were reported, and one malignancy in the reference vedolizumab IV group was reported.

Indirect Treatment Comparisons

[redacted]

The applicability of the sponsor-submitted NMA is affected by the lack of transparency in the conduction of the systematic review, the limited size of the evidence base, the potential limitations in the submitted analysis, and the heterogeneity in the design of the included studies and across populations. Additionally, there was insufficient analysis conducted to account for trial and clinical heterogeneity, thus limiting the utility and the robustness of the results. This lack of transparency in systematic review methods and analysis was considered an important limitation; as were the similar effect sizes between biologic treatments and large CrIs that resulted in an overall decrease in the confidence in the effect estimates of the NMA; any results must be interpreted with caution.

Cost and Cost-Effectiveness

Vedolizumab SC is a 108 mg/0.68 mL single-dose pre-filled syringe or pen for SC injection. The recommended dose is 108 mg every two weeks following induction with at least two 300 mg IV infusions. At the submitted price of $822.50 per pre-filled syringe or pen, the annual cost per patient at the recommended dose is estimated to be $25,501 in the first year (including two initial IV doses priced at $3,291.00 per 300 mg vial) and $21,385 thereafter.

The sponsor submitted a cost-utility analysis to assess vedolizumab SC 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. The analysis was conducted from the perspective of the Canadian publicly funded health care system over a lifetime time horizon. A cohort of both patients who are anti-TNF alpha naive and anti-TNF alpha exposed entered the model with active UC and received treatment with a biologic treatment (adalimumab, infliximab biosimilar, golimumab, vedolizumab IV, vedolizumab SC) or conventional therapy. The model structure included a decision tree to capture remission (defined as a complete Mayo score of ≤ 2 and ≤ 1 in all subscores) or response (defined as a reduction of > 3 points in the complete Mayo score and a ≥ 30% reduction in the complete score from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point) in the induction phase (10 weeks) and a Markov cohort model to capture long-term outcomes. Patients who did not respond at the end of the induction phase could either switch to conventional therapy (i.e., thereby re-entering the induction phase of the model) or undergo surgery. Patients who responded to the biologic therapy entered the Markov model in the corresponding health state (i.e., remission or response) where patients could sustain or lose remission or response and, thereby, transition to the active UC health state. Patients in the active UC state could, at any point, undergo surgery. Immediately following surgery, patients could be in the post-surgery remission or the post-surgery complications health states. Patients in the post-surgery

remission health state could transition to the post-surgery complications health state at any time within the model. Patients could further transition from any health state into an absorbing death health state, reflecting all-cause mortality. In the absence of head-to-head trial data comparing vedolizumab SC to other biologic comparators, the sponsor conducted an NMA to assess the comparative efficacy of vedolizumab SC. Utility values and resource use costs were stratified by health state. The sponsor assumed dose escalation for most of the comparators included in the analysis.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- The comparative treatment efficacy informed by the sponsor's NMA is uncertain due to a lack of transparency in the systematic review, the limited size of the evidence base, and the heterogeneity in the trial designs and patient populations.
- The probabilistic incremental cost-effectiveness ratios (ICERs) were unstable given the wide CrIs in the relative treatment effects.
- Ustekinumab and tofacitinib were excluded from the sponsor's base-case analysis.
- The probabilities, resource use, and costs of receiving surgery and post-surgery complications were overestimated.
- Resource use was not reflective of Canadian clinical practice.
- It was uncertain as to whether dose escalation within the economic model was informed by the available clinical evidence in the sponsor's NMA. The dose escalation modelled was inconsistent within the respective product monographs.

The CADTH reanalysis stratified results by anti-TNF alpha-naive and anti-TNF alpha-exposed populations. CADTH further accounted for some of the limitations by including relevant comparators; revising the probability of surgery and of post-surgery complications; adjusting costs and resource use; and removing dose escalation. Given the instability of the ICERs in the sponsor's economic model, CADTH reported deterministic results. In CADTH's base case, in the anti-TNF alpha-naive population, vedolizumab SC is dominated by tofacitinib. In the anti-TNF alpha-exposed population, vedolizumab SC had an ICER of $1,152,959 per quality-adjusted life-year gained compared with tofacitinib.

The results of CADTH's reanalysis are dependent on the sponsor's NMA, which had several methodological concerns that CADTH could not address; as such, the results of CADTH's reanalysis should be interpreted with caution.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

April 15, 2020 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None