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 Crohn disease.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that vedolizumab subcutaneous be reimbursed for the treatment of adult patients with moderately to severely active Crohn disease, only if the following conditions are met.

Conditions for Reimbursement
1. Reimburse in a similar manner to the intravenous formulation of vedolizumab.
2. Therapy with vedolizumab subcutaneous should only be initiated 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 subcutaneous injection should not exceed the drug plan cost of the least costly biologic currently reimbursed for the treatment of Crohn disease

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VEDOLIZUMAB (ENTYVIO — TAKEDA CANADA INC.)

Indication: For the treatment of adult patients with moderately to severely active Crohn disease.

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 Crohn disease, 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 initiated 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 Crohn disease.

Reasons for the Recommendation

1. In the double-blind, randomized, placebo-controlled trial (VISIBLE 2, N = 410), more patients in the vedolizumab SC group achieved clinical remission at week 52 compared with the placebo group (48.0% versus 34.3%, respectively; adjusted risk difference [RD] = 13.7%; 95% confidence interval [CI], 3.8% to 23.7%; P = 0.008). Patients in VISIBLE 2 were adults with moderately to severely active Crohn disease who achieved a clinical response at week 6 of open-label therapy with two doses of 300 mg vedolizumab IV infusion.

2. A network meta-analysis (NMA) was provided by the sponsor to evaluate the comparative efficacy of vedolizumab SC and IV with placebo and other interventions (i.e., infliximab, golimumab, adalimumab, tofacitinib, and ustekinumab) for the treatment of moderate to severely active Crohn disease (those both anti–tumour necrosis factor [TNF] naïve or experienced). [redacted] The limitations of the sponsor-submitted NMA include the limited size of the evidence base, the limitations in the submitted analysis, and the heterogeneity in the design of the included studies and across populations. Additionally, there were insufficient analyses conducted to account for trial and clinical heterogeneity, thus limiting the utility and the robustness of the results.

3. Vedolizumab SC (average annual costs of treatment are $26,320 and $21,458 per patient in the first and subsequent years, respectively) would increase costs to drug plans when compared to the least costly biologic for this indication based on publicly available prices for infliximab biosimilar ($15,776 and $12,862 per patient in the first and subsequent years). Given the uncertainty regarding the comparative effectiveness of vedolizumab SC with other biologics, there is insufficient evidence to justify a cost premium over the least expensive biologic reimbursed for the treatment of moderate to severe Crohn disease.

Discussion Points

- CDEC discussed the potential that a SC mode of administration would be preferred by patients. A conclusion on benefit on health-related quality of life (HRQoL) with vedolizumab SC treatment could not be made because the outcome measures were analyzed as exploratory outcomes and outside of the statistical analysis procedure to adjust for multiple comparisons in VISIBLE 2.
- CDEC noted that there is insufficient evidence regarding the longer-term efficacy and safety of vedolizumab SC for Crohn disease, a chronic condition.
- 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, [redacted] of the clinical or therapeutic subgroups precluded a proper interpretation of the data because they [redacted].

- CDEC noted that although it is proposed that vedolizumab's mechanism of action 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 Crohn disease.

Background

Vedolizumab SC (and IV) has Health Canada indications for:

- the treatment of adult patients with moderately to severely active Crohn disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids
- the treatment of adults 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.

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody that binds exclusively to the alpha 4 beta 7 integrin on pathogenic gut-homing lymphocytes, acting as a gut-selective anti-inflammatory biologic. Vedolizumab has no known systemic immunosuppressive effects. It is available as powder for solution for IV infusion, 300 mg per vial, and solution for SC injection, 108 mg per 0.68 mL pre-filled syringe or pen. The SC formulation of vedolizumab is the focus of the current review. It is meant to be used in the maintenance phase of treatment at 108 mg every two weeks after induction with the IV formulation.

Submission History

Vedolizumab SC has been previously reviewed by CADTH for the treatment of ulcerative colitis. The following recommendations were previously issued by CDEC in May 2020:

- vedolizumab SC be reimbursed for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist (CDEC Final Recommendation, May 19, 2020).

Vedolizumab IV has been previously reviewed by CADTH for the treatment of ulcerative colitis and Crohn disease. The following recommendations were previously issued by CDEC:

- 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 (CDEC Final Recommendation, July 15, 2015)
- the treatment of adult patients with moderately to severely active Crohn disease (CDEC Final Recommendation, September 21, 2016).

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a review of clinical trials of vedolizumab SC, a summary and critique of a sponsor-provided indirect treatment comparison, and a critique of the sponsor's pharmacoeconomic evaluation. The Committee also considered input from a clinical expert with experience in treating patients with Crohn disease, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups provided input for this submission: (1) the Gastrointestinal Society and (2) Crohn's and Colitis Canada. Patient perspectives were obtained from surveys, direct contact with patients affected with inflammatory bowel disease, interviews, patient roundtables, and phone, email, social media, or reports published by the patient groups. The following is a summary of key input from the perspective of the patient groups:

- The groups described how symptoms associated with Crohn disease (including within the gastrointestinal tract and outside of the gastrointestinal tract) affect the patients' physical and mental well-being. In addition, patients are constantly concerned about future flares which can be unpredictable and severely disruptive.

- Many respondents in the two groups required multiple medications over many years. Even though different treatment options are available, many patients still have difficulties achieving remission and/or adequate symptom relief.
- Both patient groups emphasized the importance of symptom relief, quality of life improvement, and achieving remission in patients with Crohn disease, as well as the importance of having access to a variety of treatment options when patients respond differently to treatment.
- Given the challenges in receiving medication for Crohn disease via infusion at clinics due to the significant time commitment and time away from work and school, a self-administered option, such as the SC formulation of vedolizumab, is desirable. Patients with comorbid conditions that create difficulty accessing appropriate IV sites also expressed similar desires.

Clinical Trials

The CADTH review included one sponsor-submitted, double-blind, randomized, placebo-controlled trial, the VISIBLE 2 study. In total, 644 patients with moderately to severely active Crohn disease were enrolled into the open-label induction phase, in which the patients received two doses of vedolizumab 300 mg IV infusions at week 0 and week 2. After induction with IV vedolizumab, 410 patients who achieved a clinical response at week 6, defined as a decrease of 70 points or more in the Crohn's Disease Activity Index (CDAI) score from baseline, were randomized to treatment with vedolizumab SC (108 mg vedolizumab SC every two weeks) or placebo in a 2:1 ratio in the 46-week double-blind maintenance phase. Randomization was stratified by concomitant use of oral corticosteroids, clinical remission status at week 6, and previous treatment failure with or exposure to TNF alpha antagonists or concomitant immunomodulator use. The primary outcome of VISIBLE 2 was the proportion of patients with clinical remission, defined as a CDAI score of 150 or lower at week 52.

In order to control for an overall type I error rate for the comparison between vedolizumab SC and the placebo for the primary and secondary end points, a hierarchical approach was applied to the statistical testing. Statistical significance was not achieved for the first of the secondary efficacy end points "enhanced clinical response at week 52"; therefore, statistical significance cannot be formally claimed for any of the end points ranked after this end point, including "corticosteroid-free remission." Attrition was high in the maintenance phase (39% in the vedolizumab SC group and 45% in the placebo group discontinued the study drug) mainly due to lack of efficacy of the intervention; this difference in missing data could bias the results. Sensitivity analyses were performed to examine the robustness of the study findings to missing data assumptions, [redacted]. Subgroup analyses were performed based on patient's baseline characteristics such as duration of Crohn disease, baseline disease activity, disease localization, clinical remission status at week 6, prior TNF alpha antagonist therapy, prior immunomodulator and TNF alpha antagonist failure, prior corticosteroid failure, and concomitant therapies. However, conclusions in regard to these subgroups are uncertain due to the [redacted] in the subgroups. In addition, subgroup analyses were exploratory in VISIBLE 2 and there was a lack of adjustment for multiplicity. All of these increase the uncertainty in result interpretation in the subgroups.

Outcomes

The Committee discussed clinical remission, enhanced clinical response, corticosteroid-free remission, and HRQoL:

- proportion of patients with clinical remission (primary efficacy end point in VISIBLE 2), defined as CDAI score of 150 or less at week 52
- proportion of patients with enhanced clinical response (a secondary efficacy end point in VISIBLE 2), defined as a decrease of 100 points or more in CDAI score from baseline at week 52
- proportion of patients with corticosteroid-free remission (a secondary efficacy end point in VISIBLE 2), defined as patients using oral corticosteroids at baseline who discontinued oral corticosteroids and are in clinical remission at week 52
- HRQoL:
  - EuroQol 5-Dimensions (EQ-5D)
  - Inflammatory Bowel Disease Questionnaire (IBDQ), a disease-specific HRQoL assessment tool.

Efficacy

In VISIBLE 2, of 410 patients enrolled in the maintenance phase, 275 were randomized to vedolizumab SC and 135 to placebo. More patients in the vedolizumab SC group achieved clinical remission at week 52 (primary efficacy end point) compared with the placebo group (48.0% versus 34.3%, respectively; adjusted RD = 13.7%; 95% CI, 3.8% to 23.7%; P = 0.008). In addition, a numerically higher enhanced clinical response at week 52 was observed in the vedolizumab SC group compared with the placebo group; however, the between-group difference did not reach statistical significance (52% versus 44.8%, respectively; adjusted RD = 7.3%; 95% CI, –3.0% to 17.5%; P = 0.167). Consequently, statistical significance cannot be formally claimed for any of the end points ranked after this end point in the hierarchy, such as corticosteroid-free remission at week 52. A numerically higher rate of corticosteroid-free remission at week 52 was reported for the vedolizumab group (45.3%) compared with the placebo group (18.2%).

For patient-reported outcomes, results of the IBDQ total score suggested improvements for both treatment groups: change from baseline was 63.3 points in the vedolizumab SC group and 55.1 points in the placebo group. It is unclear whether the between-group difference can be considered clinically meaningful. Similar results were observed for the results of EQ-5D visual analogue scale score and index score.

Harms (Safety)

Overall, there were no concerns of harms from VISIBLE 2 and its long-term extension study (Study SC-3030) in terms of adverse events (AEs), serious adverse events (SAEs), or harms of special interest. The incidence of treatment-emergent AEs was 73.5% in the vedolizumab SC group and 76.1% in the placebo group. The most common AEs were worsening of Crohn disease activity, abdominal pain, nasopharyngitis, arthralgia, and upper respiratory tract infections. The incidence of SAEs was comparable between the two groups, 8.4% in the vedolizumab SC group and 10.4% in the placebo group. The incidence of withdrawals due to AEs was higher in the placebo group (8.2%) compared with the vedolizumab SC group (4%).

Indirect Treatment Comparisons

One sponsor-submitted NMA aimed at evaluating the comparative efficacy and safety of vedolizumab SC relative to other comparators with similar indications. [redacted]

[redacted] The applicability of this NMA is impacted by the limited size of the evidence base, potential limitations in the submitted analysis, and heterogeneity in trial design and patient populations across trials.

Cost and Cost-Effectiveness

The drug acquisition cost of a 108 mg pre-filled syringe of vedolizumab SC is $822.50, leading to an annual cost per patient of $21,458 for maintenance treatment with 108 mg every two weeks.

The sponsor submitted a cost comparison assessing vedolizumab SC compared to vedolizumab IV, adalimumab, infliximab, and ustekinumab for the maintenance treatment of adult patients with moderately to severely active Crohn disease as described in the clinical section. The annual per patient maintenance cost of vedolizumab SC is greater than adalimumab ($20,492) and subsequent entry biologic infliximab ($12,862 to $13,697), with increased annual costs ranging from $967 to $8,596, and it is less than ustekinumab ($29,958), with reduced annual costs of $8,499. The cost comparison was undertaken from the drug plan perspective, which included drug acquisition costs, with a scenario analysis conducted from the health care payer perspective that included administrations costs for IV treatments.

CADTH identified the following key limitations with the sponsor's submitted cost comparison:

- Based on the quality and lack of robustness of the submitted NMA, the relative efficacy and safety of vedolizumab SC versus vedolizumab IV and other active comparators are uncertain.
- The sponsor did not consider induction costs as part of the calculation of total cost of the regimen in their submission. Given the requirement that patients receiving vedolizumab SC be initiated on vedolizumab IV, the sponsor's assumptions likely underestimate total treatment costs for the introduction of vedolizumab SC.

CADTH included the costs of induction therapy in the total cost calculation. The difference in year 1 treatment costs including induction costs compared with vedolizumab SC range from a savings of $10,425 versus ustekinumab to increased costs of $10,544 versus subsequent entry biologic infliximab (Renflexis).

CADTH reviewed vedolizumab IV in 2016 and recommended vedolizumab on the condition that the cost of treatment with vedolizumab IV should not exceed the drug plan cost of the least costly alternative biologic treatment option. A price reduction of 40% for vedolizumab IV would be required to match that of subsequent entry biologic infliximab (Renflexis). As such, a similar price reduction would be required for vedolizumab SC to remain cost neutral to vedolizumab IV.

CDEC Members

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

December 9, 2020 Meeting

Regrets

None

Conflicts of Interest

None