CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

BROLUCIZUMAB (Beovu — Novartis Pharmaceuticals Canada Inc.)
Indication: Treatment of neovascular (wet) age-related macular degeneration (nAMD)

RECOMMENDATION
The CADTH Canadian Drug Expert Committee (CDEC) recommends that brolucizumab should be reimbursed for the treatment of nAMD only if the following conditions are met.

Conditions for Reimbursement

Initiation criteria
1. Patient is diagnosed with mild-to-moderate nAMD and are treatment naive.

Discontinuation criteria
Brolucizumab should be discontinued if any of the following occurs:
1. reduction in best-corrected visual acuity (BCVA) in the treated eye to less than 15 letters (absolute) on two consecutive visits attributed to AMD in the absence of other pathology
2. reduction of BCVA of 30 letters or more compared to baseline and/or best recorded level since baseline as this may indicate either poor treatment effect or adverse event or both
3. evidence of deterioration of the lesion morphology despite treatment over three consecutive visits.

Prescribing conditions
1. Patients should be under the care of an ophthalmologist.
2. The interval between doses should be no less than eight weeks.

Pricing conditions
1. The drug plan cost of treatment with brolucizumab should not exceed the drug plan cost of the least costly treatment reimbursed for nAMD.

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1. The drug plan cost of treatment with brolucizumab should not exceed the drug plan cost of the least costly treatment reimbursed for nAMD.

Reasons for the Recommendation

1. In two non-inferiority, double-masked, active-controlled and randomized trials [HAWK (N = 1,082) and HARRIER (N = 743)], the mean difference between brolucizumab 6 mg verses aflibercept 2 mg for the primary outcome of change in BCVA from baseline to week 48 was –0.2 (95% CI, –2.1 to 1.8), and –0.7 (95% CI, –2.4 to 1.0) in HAWK and HARRIER, respectively. This result was within the non-inferiority margin. Assessment of the proportion of patients at week 48 who have gained greater than or equal to 15 letters from baseline or have a BCVA of greater than or equal to 84 letters at week 48 demonstrated a higher proportion in brolucizumab 6 mg (33.6%) than aflibercept 2 mg (25.4%) in HAWK. However, these results were numerically similar in HARRIER at 29.3% for brolucizumab 6 mg and 29.9% for aflibercept 2 mg. The proportion of patients with greater than or equal to 15 letters loss from baseline at week 48 was similar within and across trials with 6.4% and 3.8% in in the brolucizumab 6 mg groups in HAWK and HARRIER, respectively, and 5.5% and 4.8% for patients in the aflibercept groups in HAWK and HARRIER.

2. Several limitations in the sponsor's submitted indirect comparison have led to inconclusive results regarding brolucizumab's efficacy versus ranibizumab and bevacizumab. Limitations to the sponsor's submitted indirect treatment comparison (ITC) include: lack of reporting on informative items (such as Deviance Information Criterion values, graphic representation of the baseline characteristics across trials, results of the random-effects model); considerable heterogeneity in some baseline characteristics (most notably, the variation in values of retinal thickness; lack of consistency in retinal thickness assessment; and weak connection between brolucizumab and the rest of the network (as evident by the wide credible intervals).

3. CADTH's reanalysis of a cost-utility model submitted by the manufacturer found that brolucizumab was unlikely to be cost-effective at the submitted price, with costs per quality-adjusted life-year (QALY) of $583,404. Results were sensitive to the inclusion of bevacizumab as a comparator to the model.

Discussion Points

- CDEC discussed that the available studies supporting the effectiveness and safety of brolucizumab have only included treatment-naive patients with mild-to-moderate nAMD. Correspondingly, the efficacy and safety of brolucizumab is unknown in patients with previous anti–vascular endothelial growth factor (VEGF) experience.
- CDEC noted that results related to injection frequency of brolucizumab reported in the clinical trials have several limitations that potentially reduce the generalizability of the results to clinical practice. The committee noted that Health Canada's product monograph leaves the decision of an injection frequency of every eight weeks or every 12 weeks to the clinical judgment of the treating ophthalmologist.
- The current body of evidence for the efficacy and safety of brolucizumab use for nAMD lacks direct evidence comparing the effectiveness and safety of brolucizumab with other reimbursed anti-VEGF treatments for nAMD. The available indirect evidence poses a high-level of uncertainty.
- CDEC noted that there is lack of comparative effectiveness and safety data of brolucizumab beyond 96 weeks.

Background

Brolucizumab has a Health Canada indication for the treatment of nAMD. Brolucizumab is a humanized monoclonal single-chain Fv (scFv) antibody fragment directed against human VEGF. It is available as a single-use pre-filled syringe for intravitreal injection and the Health Canada–approved dose is 6 mg (0.05 mL) administered by intravitreal injection every four weeks for the first three doses, after which it can be given as one injection every 12 weeks in patients without disease activity or one injection every eight weeks in patients with disease activity, based on the physician assessment.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review of randomized controlled trials of brolucizumab, a sponsor-submitted ITC, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with nAMD, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

- CADTH received one joint patient group submission that was prepared by Fighting Blindness Canada, the Canadian Council of the Blind, the CNIB Foundation, and Vision Loss Rehabilitation Canada. Patient perspectives were obtained from a survey of 97 patients with nAMD and 60 patients with dry AMD. The following is a summary of key input from the perspective of the patient group(s): AMD is recognized as the leading cause of vision loss in people older than 50. Patients with nAMD are particularly concerned about the negative effects of central vision loss on all aspects of daily living including the ability to read, drive, interact with others, distinguish faces, navigate public spaces, travel, cook, and do work around the home. The average age of nAMD respondents in the patient survey was 78 years and the loss of independence in this age group can have a profound negative impact on quality of life.
- Most patients were satisfied with the effectiveness of current treatment options.
- Most patients expressed a preference for therapies with less frequent administration.
- Many patients with vision loss have limited access to transportation to receive treatments, a problem compounded for those living in areas without major treatment centres.
- Patients noted their expectations of having fewer injections with brolucizumab.

Clinical Trials

The systematic review included two phase III, non-inferiority, multi-centre, double-masked, active-controlled, parallel, and randomized trials in patients with nAMD. These studies were HAWK (N = 1,082) and HARRIER (N = 743), and each trial had a study duration of 96 weeks. In HAWK, 1,082 patients with nAMD were randomized in a 1:1:1 ratio to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg. In HARRIER, 743 patients with nAMD were randomized in a 1:1 ratio to brolucizumab 6 mg or aflibercept 2 mg. All patients received three monthly loading intravitreal injections followed by maintenance doses every 12 weeks for brolucizumab and every eight weeks for aflibercept. Patients on the brolucizumab every 12 weeks regimen could be permanently switched to an injection frequency of every eight weeks if an investigator determined the presence of continuous disease activity based on pre-specified criteria.

Limitations of the HAWK and HARRIER studies include lack of stratification for geographic region, adjustment for multiplicity in HARRIER, and potential risk of unmasking treatment assignment through the use of sham injection and an unmasked injection physician. In addition, generalizability of the result is limited to a treatment-naive population. Also, the applicability of the results measuring the proportion of patients receiving every eight weeks or every 12 weeks regimens might be limited in practice due to lack of validation of the disease activity assessment tool, and the common use of treat-and-extend dosing protocol in clinical practice. Finally, no direct evidence comparing brolucizumab with ranibizumab or bevacizumab is available.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: change from baseline in BCVA on week 48 and week 96 measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, proportion of patients who gained 15 or more ETDRS letters on week 48 and week 96, changes in retinal thickness from baseline to week 48 and 96, and health-related quality of life measured through the Visual Function Questionnaire (VFQ-25) composite score. In addition, CDEC discussed time-to-first every-eight-weeks outcome among patients who received brolucizumab. The primary outcome in HAWK and HARRIER was change in BCVA from baseline to week 48.

- ETDRS charts present a series of five letters of equal difficulty on each row, with standardized spacing between letters and rows, for a total of 14 lines (70 letters). ETDRS letter score can be calculated when 20 or more letters are read correctly at 4.0 metres; the visual acuity letter score is equal to the total number of letters read correctly at 4.0 metres plus 30. A loss or gain of three lines (15 letters) is considered a moderate degree of change and is commonly used as an outcome in clinical trials.
- The National Eye Institute (NEI) VFQ was developed as a means to measure vision-targeted quality of life. The VFQ-25 includes 25 items relevant to 11 vision-related constructs, in addition to a single-item general-health component. Responses for each item are converted to a 0 to 100 scale, with 0 representing the worst, and 100 the best visual functioning. Items within each construct, or subscale, are averaged to create 12 subscale scores, and averaging of the subscale scores produces the overall composite score. Determination of what constitutes a clinically meaningful change in the VFQ-25 appears to be linked to its correlation with visual acuity. A three-line (15-letter) change in visual acuity has been used as the outcome of interest in clinical trials, and corresponding changes in the VFQ-25 are suggested as clinically meaningful end points. Based on correlation with the 15 ETDRS letters change in previous macular edema trials, a clinically relevant difference for the VFQ-25 composite score was suggested to be 7.35 to 8.18 points.

Efficacy

The treatment group differences in both studies were within the non-inferiority margin. In HAWK, the mean difference of brolucizumab 6 mg verses aflibercept 2 mg was –0.2 (95% CI, –2.1 to 1.8), and in HARRIER it was –0.7 (95% CI, –2.4 to 1.0). Sensitivity analyses reported by the sponsor showed similar results to the base case. Results at week 96 indicate that the improvement reported at week 48 were maintained. Assessment of the proportion of patients at week 48 who have gained greater than or equal to 15 letters from baseline or have a BCVA of greater than or equal to 84 letters at week 48 show a higher numerical proportion in brolucizumab 6 mg (33.6%) than aflibercept 2 mg (25.4%) in HAWK. However, these results are numerically similar in HARRIER at 29.3% for brolucizumab 6 mg and 29.9 for aflibercept 2.0 mg. On the other hand, the proportion of patients with greater than or equal to 15 letters loss from baseline at week 48 was similar within and across trials with 6.4% and 3.8% in the brolucizumab

6 mg groups in HAWK and HARRIER, respectively, and 5.5% and 4.8% for patients in the aflibercept groups in HAWK and HARRIER, respectively.

Anatomical related outcomes of retinal thickness and the proportion of patients with subretinal or intraretinal fluids show statistically significant improvements in patients treated with brolucizumab 6 mg compared to patients treated with aflibercept in the HAWK study at week 48. These findings are supported numerically by the results on the HARRIER study. Other outcomes show numerically similar results within and across studies, including the VFQ-25 composite score.

By the end of the first year, almost half of the patients randomized to brolucizumab had been switched to the every-eight-week regimen. The majority of the patients who were switched to every-eight-week dosing were identified at week 16 and week 20.

Harms (Safety)

- In HAWK, 61.1% of patients treated with brolucizumab 6 mg had at least one ocular adverse event, while 55.8% of patients treated with aflibercept had at least one ocular adverse event. In HARRIER, 47.0% of patients treated with brolucizumab had at least one ocular adverse event, while 47.7% of patients treated with aflibercept had at least one ocular adverse event.
- In HAWK, 3.3% of patients treated with brolucizumab 6 mg had at least one ocular serious adverse event, while 1.4% patients treated with of aflibercept had at least one ocular serious adverse event. In HARRIER, 3.5% of patients treated with brolucizumab had at least one ocular adverse event, while 1.6% of patients treated with aflibercept had at least one ocular adverse event.
- Overall, 3.1% and 3.5% of the patients in the brolucizumab arms permanently discontinued treatment in each of the HAWK and HARRIER studies, respectively. Of the patients in the aflibercept arms, 3.3% and 1.6% permanently discontinued treatment in each of the HAWK and HARRIER studies, respectively.
- Eye inflammation-related adverse events showed a numerically higher proportion of patients affected in the brolucizumab group compared to the aflibercept group.

Indirect Treatment Comparisons

One indirect treatment comparison (ITC) was submitted by the sponsor and included in this review, no additional ITCs were identified in the literature. The sponsor performed a network meta-analysis (NMA) to estimate the efficacy of brolucizumab in patients with nAMD against other anti-VEGFs. The authors of the sponsor-submitted ITC used a Bayesian approach through the Monte Carlo Markov chains simulation. Non-informative priors were chosen for the analysis. For the outcome of BCVA at one year, the authors analyzed 21 trials under a fixed-effects model.

In the ITCs, brolucizumab 6 mg once every 12 weeks or once every eight weeks was significantly better than sham. Comparison between brolucizumab 6 mg and all other comparators included zero in the 95% credible interval (CrI). Also, wide CrIs were noted in several comparisons. At two years, the network for the BCVA outcome was much sparser than at one year as it included nine trials. Similar to the one-year results, brolucizumab was significantly better than sham, but wide CrIs were more prominent at the two years outcome than at the one-year outcome. For the outcome of retinal thickness, at one year, the authors analyzed 18 randomized controlled trials under a fixed-effects model. The results showed brolucizumab to be significantly better against all comparators except for the comparison against ranibizumab 0.5 mg as needed with extension and a loading phase, and versus brolucizumab 3 mg once every 12 weeks or once every eight weeks with a loading phase. However, CrIs in these results are notably large in all of the results. At two years, the authors analyzed eight trials with the results showing larger CrIs than the one-year and null results included in comparisons that were significant in the one-year analysis.

Limitations to the sponsor's ITC include: lack of reporting on informative items (such as Deviance Information Criterion values, graphic representation of the baseline characteristics across trials, and results of the random-effects model); considerable heterogeneity in some baseline characteristics (most notably is the variation in the values of the retinal thickness and in the method of assessing retinal thickness); lack of inconsistency assessment; and weak connection between brolucizumab and the rest of the network with only one study directly informing the network (as also evident by the wide CrIs). These limitations pose a considerable challenge in making a conclusive decision regarding the validity of the results to inform clinical practice.

Cost and Cost-Effectiveness

Brolucizumab is available as a 120 mg/mL pre-filled syringe, at a submitted price of $1,418 per syringe. The recommended dose is 6 mg administered by intravitreal injection every four weeks for the first three doses, and every 12 weeks thereafter. The annual per-patient drug acquisition cost of brolucizumab is $8,508 in the first year and $5,672 in subsequent years

The sponsor submitted a cost-utility analysis comparing brolucizumab as initial treatment for the treatment of nAMD with aflibercept and ranibizumab. At CADTH's request, an economic model with bevacizumab included was provided. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a lifetime time horizon. The pharmacoeconomic submission was based on a Markov model that was comprised of a total of 13 mutually exclusive health states: six health states were divided according to the level of BCVA in a single eye for both "on-treatment" and "off-treatment" patients. BCVA was measured using the number of ETDRS letters. All patients enter the model in the "on-treatment" health states (distribution informed by the HAWK and HARRIER trials) and could experience one of five scenarios annually: maintain the current BCVA health state, transition by one BCVA health state (a lower or higher number ETDRS letters), transition by two BCVA health states, discontinue treatment and transition to "off-treatment," or proceed to death from any health state. The relative treatment effects (mean change in BCVA) for all included therapies were derived from the sponsor-submitted NMA using aflibercept as the reference arm. In the sponsor's base case, brolucizumab dominated both aflibercept and ranibizumab (it was associated with fewer costs and increased QALYs).

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

- Bevacizumab was excluded from the sponsor's base-case economic model; however, given that multiple public drug programs reimburse treatment with bevacizumab for nAMD, CADTH considered this to be a relevant comparator.
- Discontinuation rates differed between anti-VEGF inhibitors based on outputs from the sponsor's NMA; however, CADTH considered equal discontinuation to be more appropriate based on feedback from the clinical experts consulted for this review.
- Costs associated with vision loss were overestimated as it was uncertain that these costs represented only those related to the health system (aligned with the analysis perspective) and adequately captured costs specific to nAMD.
- The treatment effect was assumed to be maintained beyond three years. CADTH considered this assumption to be overtly optimistic and that it was associated with uncertainty given the lack of long-term data.
- The sponsor included vision loss-adjusted mortality; however, this was not appropriately implemented in the economic model and the study results used to generate mortality estimates may not be applicable to the HAWK or HARRIER trial populations, adding uncertainty to the cost-effectiveness results.
- Treatment switching and discontinuation criteria were not analyzed in the economic model, limiting inference for different reimbursement decisions and clinical practice.

CADTH undertook reanalyses to address the identified limitations: including subsequent entry biologic (SEB) bevacizumab in the revised base case, applying equal discontinuation rates, adjusting costs of vision loss, and applying a pooled treatment effect for the long-term extrapolation. CADTH could not explore the impact of different discontinuation criteria and some structural limitations remained within the model.

Based on sequential analyses using the CADTH base case, the incremental cost-effectiveness ratio for brolucizumab compared with bevacizumab was $583,404 per QALY. Brolucizumab dominated ranibizumab (produced more QALYs at a lower cost) and the sequential incremental cost-effectiveness ratio for aflibercept compared with brolucizumab was $2,862,068 per QALY. At a willingness-to-pay threshold of $50,000 per QALY, a price reduction of 85% is required for brolucizumab to be considered cost-effective when compared to the SEB bevacizumab. No price reduction would be required for brolucizumab if bevacizumab is unavailable.

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