Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Aflibercept 8 mg/0.07 mL (Eylea HD)

Indication: For the treatment of neovascular (wet) age-related macular degeneration

Sponsor: Bayer Inc.

Recommendation: Reimburse with Conditions

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Single Technology

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that aflibercept 8 mg/0.07mL be reimbursed for the treatment of neovascular (wet) age-related macular degeneration (nAMD) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One randomized, double-blind, active-controlled, phase III trial (PULSAR, N = 1,009) demonstrated that aflibercept 8 mg every 12 weeks and every 16 weeks was noninferior to aflibercept 2 mg every 8 weeks in improving best corrected visual acuity (BCVA) from baseline over 48 weeks of treatment in treatment-naïve adult patients with nAMD. The difference between treatment arms in the least squares (LS) mean change (improvement) from baseline to week 48 was -0.97 (95% confidence interval [CI], -2.87 to 0.92) letters for aflibercept 8 mg every 12 weeks versus 2 mg every 8 weeks (non-inferiority p = 0.0009; superiority p = 0.8437) and -1.14 (95% CI, -2.97 to 0.69) letters for 8 mg every 16 weeks versus 2 mg every 8 weeks (non-inferiority p = 0.0011, superiority p = 0.8884). In the absence of direct comparative evidence versus other currently available treatments for nAMD, results from a network meta-analysis (NMA) that compared aflibercept 8 mg to other anti-vascular endothelial growth factor (VEGF) treatments for nAMD suggested uncertainty about what treatment might be favoured for visual acuity outcomes because point estimates were nearby the null, with wide credible intervals.

Patients expressed a need for new treatments for nAMD that, as well as being effective and safe, require fewer injections. In the PULSAR trial, the between-group difference in the mean numbers of active injections through week 48 between aflibercept 2 mg every 8 weeks and aflibercept 8 mg every 12 weeks was -0.9 (95% CI, [redacted]) injections and the difference between aflibercept 2 mg every 8 weeks and aflibercept 8 mg every 16 weeks was -1.8 (95% CI, [redacted]) injections. However, given the lack of statistical testing for this outcome, the risk of bias due to missing data, and the potential difference in number of injections driven by the trial protocol compared to clinical practice, this evidence was uncertain. There were no indirect comparisons versus other anti-VEGF drugs used to treat nAMD provided for injection frequency, aside from naïve (visual) comparison of pairwise meta-analyses for each regimen.

Due to limitations in the comparative efficacy evidence from the sponsor's indirect treatment comparison (ITC), it was not possible to estimate the incremental cost-effectiveness of aflibercept 8 mg relative to any other comparator treatment. At the sponsor submitted price for aflibercept 8 mg and publicly listed prices for other comparator regimens, aflibercept had higher drug acquisition costs than bevacizumab, and lower drug acquisition costs than all other comparators reimbursed for the treatment of nAMD. Therefore, aflibercept 8 mg should be negotiated so that it does not exceed the drug program cost with the least costly comparator reimbursed for the treatment of nAMD.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults with nAMD who meet all of the following criteria: 1.1. Treatment-naïve to anti-VEGF drugs for nAMD; 1.2. BCVA ETDRS letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320); 1.3. Total area of CNV comprises >50% of total lesion area in the eye; 1.4. Presence of IRF and/or SRF affecting the central subfield on OCT.	The PULSAR trial showed that aflibercept 8 mg was effective in adult patients with treatment-naïve active CNV lesions secondary to nAMD (>50% of the total lesion area), BCVA ETDRS letter scores of 78 to 24 (Snellen equivalent of 20/32 to 20/320), and with IRF and/or SRF affecting the central subfield on OCT.	Aflibercept 8 mg could be initiated in a similar manner to other anti-VEGF drugs for nAMD as per the reimbursement criteria for each public drug plan.
2. The maximum duration of initial authorization is 6 months.	This is to help ensure that aflibercept 8 mg is used in patients who benefit from treatment.	—
Renewal		
3. For renewal after initial authorization, patients must achieve at least 15 letters improvement in BCVA at 6 months compared with baseline (pre-treatment).	A CADTH therapeutic review of anti-VEGF drugs for the treatment of retinal conditions found that an inadequate response to treatment can be defined as not achieving any improvement in BCVA at 3 months or not achieving an improvement in BCVA at 6 months of at least 15 ETDRS letters compared with the baseline (pre-treatment) BCVA. At 6 months, patients would have received the first 3 consecutive doses of aflibercept 8mg every 4 weeks and an additional injection based on a 12- or 16-week interval between injections.	—
Discontinuation		
4. Aflibercept 8 mg should be discontinued upon any of the following: 4.1. Reduction in BCVA in the treated eye to less than 15 letters (absolute) on 2 consecutive visits in the treated eye, attributed to AMD in the absence of other pathology; 4.2. Reduction in BCVA of 30 letters or more compared to either baseline and/or best recorded level since baseline; 4.3. Evidence of deterioration of the lesion morphology	This is to ensure that aflibercept 8 mg is being used in patients who are benefiting from treatment.	Aflibercept 8 mg could be discontinued in a similar manner to other anti-VEGF drugs for nAMD as per the reimbursement criteria for each public drug plan.

Reimbursement condition	Reason	Implementation guidance
despite optimum treatment over 3 consecutive visits.		
Prescribing		
5. The patient should be under the care of an ophthalmologist with experience in managing nAMD.	To ensure that aflibercept 8 mg is prescribed for appropriate patients and administered by a trained ophthalmologist.	Aflibercept 8 mg could be prescribed in a similar manner to other anti-VEGF drugs for nAMD as per the reimbursement criteria for each public drug plan.
6. Aflibercept 8 mg should not be prescribed in combination with other anti-VEGF drugs.	There was no submitted evidence to support combination use of anti-VEGF drugs.	—
7. Injections should not be given more frequently than every 12 weeks after the first 3 consecutive doses.	In the PULSAR trial, aflibercept 8 mg every 12 weeks and 16 weeks after 3 initial injections at 4-week intervals demonstrated non-inferiority (but not superiority) to aflibercept 2 mg every 8 weeks. Treatment intervals of 1 month (4 weeks) for more than 3 consecutive doses have not been studied.	—
Pricing		
8. Aflibercept 8 mg should be negotiated so that it does not exceed the drug program cost of treatment with the least costly anti-VEGF reimbursed for the treatment of nAMD.	Results from a NMA that compared aflibercept 8 mg to other anti-VEGF treatments for nAMD suggested uncertainty about what treatment might be favoured for efficacy outcomes (visual acuity) because point estimates were nearby the null, with wide credible intervals. As such, there is insufficient evidence to justify a cost premium for aflibercept 8 mg over the least expensive anti-VEGF reimbursed for nAMD.	—

BCVA = best corrected visual acuity; ETDRS = Early Treatment of Diabetic Retinopathy Study; IRF = intraretinal fluid; nAMD = neovascular (wet) age-related macular degeneration; NMA = network meta-analysis; OCT = optical coherence tomography; SRF = subretinal fluid; VEGF = vascular endothelial growth factor.

Discussion Points

- The GRADE assessment of selected outcomes from the PULSAR trial's evidence concluded with high certainty that aflibercept 8 mg every 12 and 16 weeks demonstrates non-inferiority (but not superiority) to aflibercept 2 mg every 8 weeks in terms of the change (improvement) in BCVA from baseline over 48 weeks of treatment among treatment-naive adult patients with nAMD. Moderate certainty evidence showed that aflibercept 8 mg every 12 and 16 weeks likely results in little-to-no difference in important outcomes such as the proportion of patients gaining ≥15 letters in BCVA and vision-related QoL when compared with aflibercept 2 mg every 8 weeks. Moderate certainty evidence suggested aflibercept 8 mg every 12 weeks and every 16 weeks likely results in little-to-no difference in the risk of ocular serious adverse events (SAEs) when compared with aflibercept 2 mg every 8 weeks at 60 weeks.
- CDEC noted that frequency of injections was identified as an important outcome to both patients and clinicians because it potentially has implications for burden of treatment, adverse events (AEs), and vision-related quality of life (QoL). The evidence from the PULSAR trial suggests that aflibercept 8 mg every 16 weeks may reduce the frequency of injections at 48 weeks. However, these results are associated with low certainty as per the GRADE assessment because of risk of bias due to missing outcome data as well as indirectness due to the number of injections being driven by the trial protocol. Furthermore, CDEC noted the decreased frequency of injections observed in the PULSAR trial may not be realized in

clinical practice in Canada – the PULSAR trial's protocol-specified dosing interval of every 8 weeks for the aflibercept 2 mg arm was not aligned with the treat-and-extend protocol commonly used with aflibercept 2 mg in clinical practice.

- CDEC noted two gaps in the submitted evidence. First, the limitations of the ITC precluded CDEC from drawing conclusions regarding the efficacy of aflibercept 8 mg every 12 weeks or every 16 weeks when compared to other anti-VEGF drugs. Second, CDEC noted that PULSAR trial enrolled treatment-naïve patients with nAMD, therefore the comparative efficacy and harms of aflibercept 8 mg versus other anti-VEGF drugs in patients with previous anti-VEGF experience is a gap in the submitted evidence.
- Regarding the pricing condition, CDEC discussed considerations regarding identifying the least costly comparator due to the potential introduction of biosimilars and off-label comparator use. Biosimilars for aflibercept are currently under review by Health Canada, and so at the time of this review, the comparative cost and cost-effectiveness of aflibercept 8 mg relative to biosimilars of anti-VEGF drugs is unknown. Additionally, CDEC discussed that bevacizumab was the lowest cost comparator included in the review and noted that it is used off label, without an indication for the treatment of nAMD. CDEC recognized that drug plans may or may not consider bevacizumab a relevant comparator in their negotiations.

Background

Age-related macular degeneration (AMD) is a progressive condition characterized by central vision loss due to ageing. Neovascular (wet) AMD (nAMD) is a late-stage version of AMD, affecting about 10% of patients and accounts for 90% of severe vision loss in Canada. The overall prevalence of any AMD in Canada is estimated at 9% among adults aged 45 years and older, with about 10% of patients reportedly presenting with the neovascular form. Age-related macular degeneration affects over 2.5 million Canadians, with about 180,000 patients experiencing vision loss. Patients experience rapid vision loss with worsening of central vision (caused by scotoma) and/or distortion of straight lines. If left untreated, nAMD produces scarring and irreversible vision loss. Prompt treatment is imperative, given that patients who experience treatment delay have lower chances of visual outcome improvement. Thus, patients with impaired visual acuity caused by progressive disease will experience difficulties with daily living, an increased risk of falls, and are at higher risk of social dependence and premature admission to nursing homes.

The clinical expert consulted by CADTH indicated that intravitreal injections with anti-vascular endothelial growth factor (VEGF) therapies have become the current standard of care for nAMD including aflibercept 2 mg, ranibizumab, brolucizumab, and faricimab. Bevacizumab is an off-label treatment for this condition. Anti-VEGF therapies are recommended as the first line treatment by guidelines from international ophthalmology societies including the Canadian Retina Society, American Academy of Ophthalmology, the European Retina Society and the British Royal College of Ophthalmology. The clinical expert consulted by CADTH noted that there are different treatment strategies currently in practice for the management of nAMD including a fixed dosing regimen, Pro Re Nata (PRN) regimen, or treat and extend regimen.

Aflibercept 8 mg/0.07 ml is indicated for the treatment of nAMD. Aflibercept is an anti-VEGF drug, which inhibits predominant signaling pathways responsible for angiogenesis and vascular leakage: VEGF-A and placental growth factor (PIGF). The recommended dosage is administered by intravitreal injection every month (4 weeks +/- 1 week) for the first 3 consecutive doses, followed by 8 mg (0.07 mL) every 8 to 16 weeks (plus or minus 1 week) based on the physician's judgement of visual and anatomic outcomes.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III randomized controlled trial in patients with nAMD and 1 sponsor-submitted ITC
- patients' perspectives gathered by 2 patient groups, Canadian Council of the Blind (CCB), and a joint input from Fighting Blindness Canada, the Canadian Council of the Blind, Vision Loss Rehabilitation Canada, and the International Federation on Ageing (IFA)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- one of clinical specialist with expertise diagnosing and treating patients with nAMD
- input from 6 clinician groups, including the Southwestern Ontario Community Ophthalmologists, Toronto Retina Institute, the Canadian Retina Society, Retina Division of the Ottawa Hospital, the Northeastern Ontario Ophthalmology Group, Toronto Ophthalmologists
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Input was received from the Canadian Council of the Blind (CCB) and a joint input from Fighting Blindness Canada, the Canadian Council of the Blind, Vision Loss Rehabilitation Canada, and the International Federation on Ageing (IFA). They surveyed patients living with nAMD including 337 people in Canada.

Vision loss due to AMD has substantial and life-altering impacts on patients' daily life, manifesting as physical, psychological, and social impacts, according to the patient groups. Patients expressed they often relied on assistance from others to attend

appointments and felt isolated or lonely. Patients worried over their condition worsening due to missed injection appointments. The patient groups noted that burden associated with injection appointments increased when they were frequent.

There were no patients surveyed that had experience with the drug under review. Respondents indicated they were satisfied with their current therapies and expressed that it helped them avoid losing more eyesight. According to the patient groups, a treatment that is efficacious and reduces the number of visits to the ophthalmologist (i.e., a treatment that requires fewer injections) will undoubtedly lead to fewer missed appointments and improve outcomes.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert indicated that the cost of travelling to medical appointments and the burden on family members for assistance are some of the obstacles that limited older adult patients with nAMD to have an optimal treatment outcome. Therefore, a drug or treatment program that allows less frequent visits is an important option to improve patient compliance to fill this treatment gap. The clinical expert highlighted the newer emerging anti-VEGF agents, faricimab and brolucizumab, can extend the treatment interval to 12 weeks, even up to 16 weeks. However, the clinical expert reported that brolucizumab is associated with intraocular inflammation. Therefore, the clinical expert concluded a more durable treatment with high efficacy and without the increase of adverse side effects is an unmet need.

The clinical expert noted that the introduction of longer acting therapy represents a treatment paradigm shift. The expert indicated that aflibercept 2 mg has been used over 10 years with known safety profile. The clinical expert noted that aflibercept 8 mg could be considered as first-line treatment for nAMD. In addition, the clinical expert indicated that it could be considered as replacement therapy when the other anti-VEGF treatments are ineffective or for treatment of those who do not respond with the other anti-VEGF treatments.

Clinical expert consulted by CADTH noted that the outcome measures used in clinical practice align with those in the trial: visual acuity; optical coherence tomography (OCT) to assess intraretinal or subretinal fluid; central retinal thickness measurement; and fundus examination for retinal or subretinal hemorrhage. Following the initial monthly aflibercept 8 mg treatment for 3 months, the treatment interval can be extended to every 12 weeks, and subsequently, the interval can be adjusted by increments or reductions of 4 weeks for the next treatment cycle. Clinical expert indicated the features of treatment failure are decreasing visual acuity, the persistent or increase intraretinal or subretinal fluid, or development of new subretinal hemorrhage despite active treatment. The clinical expert noted the treatment with aflibercept 8 mg can be given in the clinic or hospital. The treatment should be provided by an ophthalmologist who is familiar with the diagnosis and management of retinal diseases including nAMD.

Clinician Group Input

Southwestern Ontario Community Ophthalmologists, Toronto Retina Institute, the Canadian Retina Society, Retina Division of the Ottawa Hospital, the Northeastern Ontario Ophthalmology Group, Toronto Ophthalmologists provided input to this review.

Treatment goals highlighted for AMD were consistent across groups (i.e., to maintain vision while extending the duration between treatments to reduce the treatment burden). The clinician groups highlighted that although current treatments (anti-VEGFs) target the underlying disease mechanism, they are not curative, and the extent and duration of damage to the retina may impact their ability to achieve improvement. Therefore, there is a need for new treatments that are efficacious and durable, improve long-term visual outcomes, and maintain a favorable safety profile that minimizes the risk of ocular complications. They agreed that a treatment formulation designed and studied with an extended dosing interval would help address the high burden of repeated injections for patients, caregivers, ophthalmologists, and reduce backlogs in the health care system. One group added that a treatment that promotes fluid-free retina for longer durations will allow improved quality of life metrics that have been associated with vision loss secondary to nAMD. The clinician groups anticipate that aflibercept 8 mg will replace the aflibercept 2 mg formulation, establishing it as a new first-line treatment choice for AMD. The clinician groups inputs aligned with the input submitted by the clinical expert consulted for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
PULSAR is a phase 3, multi-centre, randomised, double-masked, active-controlled study that compared aflibercept high dose (8mg) to aflibercept 2 mg for efficacy, safety, and tolerability and to determine if aflibercept 8 mg administered in two extended dosing regimens was non-inferior to aflibercept 2 mg. There were no trials comparing aflibercept 8mg with other anti-VEGF drugs (brolucizumab and faricimab) that can be administered at the same extended dosing interval.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
Most provinces have retinal programs and therefore no published criteria or criteria is not adjudicated against. Some provinces have initiation criteria that was developed by a working group and may be outdated. Inclusion criteria for PULSAR are not consistent with existing drug plan criteria for nAMD. Ranibizumab recommendation is from 2008 with no initiation or discontinuation criteria. Aflibercept 2 mg recommendation is from 2014 and also did not include initiation or discontinuation criteria. More recently, the brolucizumab recommendation included wording from existing drug plan criteria (discontinuation criteria), and faricimab was to list in a similar manner to other anti-VEGF drugs.	The clinical expert consulted by CADTH advised that the initiation of treatment for patients diagnosed with nAMD, defined by the presence of retinal fluid (either intraretinal or subretinal) or hemorrhages, is warranted. In terms of discontinuing treatment, the clinical expert consulted by CADTH noted that several factors should be considered, such as the absence of a positive response in a patient after receiving the treatment for at least three interval injections, as well as a lack of improvement in retinal fluid or visual acuity. In such cases, the clinical expert suggested that it is advisable to contemplate switching or discontinuing the medication, as it may not be delivering the intended benefits, while acknowledging that each injection carries inherent risks. Conversely, the clinical expert noted that patients at the end stages of the disease with extensive scarring are unlikely to derive significant benefits from anti-VEGF treatment. Therefore, this also warrants consideration in terms of treatment cessation.
Considerations for discontinuation of therapy	
Consistency with discontinuation criteria associated with other drugs reviewed by CADTH in the same therapeutic space.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
The manufacturer notes that aflibercept 8 mg meets an unmet need by having a dosing frequency of every 12 to 16 weeks. Recommended dose of brolucizumab is 6 mg every 6 weeks for the first 5 doses then every 12 weeks. Recommended dose of faricimab is 6 mg every 4 weeks for the first 4 doses then every 8, 12 or 16 weeks.	This is a comment from the drug programs to inform CDEC deliberations
Does aflibercept 8 mg meet an unmet need given there are other products marketed with an extended dosing interval?	The clinical expert consulted by CADTH indicated that currently, there are three medications that offer extended dosing intervals: aflibercept 8 mg, faricimab, and brolucizumab. The clinical expert

Implementation issues	Response
	indicated that it is essential to note that brolucizumab has been associated with a higher frequency of intraocular inflammations and severe cases of hemorrhagic retinal vasculitis. These severe effects have the potential to cause significant vision loss, to the extent that some patients may even experience complete blindness as a result of complications arising from the treatment. The clinical expert noted that faricimab represents a relatively newer medication that can extend treatment intervals up to 12 weeks. While it's not clear if the intention is to extend treatment to 16 weeks, this 16-week extension is the optimal treatment goal. This is noteworthy because even aflibercept 2 mg, in some cases, allows for extension up to 12 weeks when using a treat and extend protocol. The clinical expert noted that aflibercept 2 mg, with a history of over a decade in clinical use, demonstrated an appropriate safety profile The clinical expert highlighted that the primary objective, as dictated by the unmet need, is to extend treatment intervals and alleviate the treatment burden on both patients and clinicians.
System and economic issues	
Aflibercept 8mg would have significant budget impact on public drug plans. Biosimilars have already been marketed for ranibizumab. Biosimilars are anticipated for aflibercept 2 mg next year. Public drug plans have expressed concerns regarding brand manufacturers marketing an improved version of an existing originator drug to maintain market share and to extend a product's patent. There has been a significant increase in drug utilization in some jurisdictions for aflibercept 2 mg due to prescriber switching from ranibizumab. It is expected that this would occur with aflibercept 8mg. Should the pricing recommendation for reimbursement recommend that aflibercept 8mg be negotiated so that it provides cost savings to drug programs relative to the cost of currently funded anti-VEGF drugs for AMD?	Refer to pricing condition in Table 1.
Confidential pricing agreements exist for most anti-VEGF drugs. Based on current list price, aflibercept 8mg is not a cost-effective treatment option.	This is a comment from the drug programs to inform CDEC deliberations

AMD = age-related macular degeneration; CDEC = CADTH Canadian Drug Expert Committee; nAMD = neovascular age-related macular degeneration; NB= New Brunswick; VEGF = vascular endothelial growth factor

Clinical Evidence

Systematic Review

Description of Studies

PULSAR (N=1009) was a phase 3, multicenter (3 sites in Canada), double-blind, randomized, active-controlled non-inferiority trial to demonstrate the efficacy and safety of aflibercept 8 mg every 12 weeks and aflibercept 8 mg every 16 weeks compared to aflibercept 2 mg every 8 weeks in adult treatment-naïve patients with nAMD. The study included a screening period (up to 3 weeks)followed by a treatment period. Outcomes were assessed at the 48-week and 60-week time points of the treatment period. The primary outcome of PULSAR was the change from baseline in best corrected visual acuity (BCVA) at 48 weeks. Secondary outcomes that were relevant to the review included the proportion of patients with no intraretinal fluid (IRF) and no subretinal fluid (SRF) at week 48, proportion of participants gaining at least 15 letters in BCVA from baseline at week 48, frequency of injection through week 48, change from baseline in National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) total score at week 48, treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) through week 60.

The overall proportion of male and female participants was 45.5% and 54.5%, respectively. The median age was 75 years, ranged from 50 to 96 years, and the majority of participants were White (75.8%) or Asian (23.2%). Most patients had a baseline BCVA of ≤73 letters on ETDRS charts (86.2%).

Efficacy Results

Change from Baseline in BCVA at Week 48

The difference in LS mean change from baseline (95% CI) to week 48 was -0.97 (-2.87 to 0.92) letters for 8 mg every 12 weeks vs. 2 mg every 8 weeks (non-inferiority p = 0.0009; superiority p = 0.8437) and -1.14 (-2.97 to 0.69) letters for 8 mg every 16 weeks vs. 2 mg every 8 weeks (non-inferiority p = 0.0011, superiority p=0.8884). Results of analysis of the PPS and sensitivity analyses using different missing data imputation approaches were consistent with those in the FAS. The differences in LS mean change from baseline (95% CI) to week 60 were -0.86 (-2.57 to 0.84) letters (non-inferiority p = 0.0002; superiority p = 0.8393) and -0.92 (-2.51, 0.66) letters (non-inferiority p <0.0001; superiority p = 0.8371) for the 8 mg every 12 weeks and 8 mg every 16 weeks arms, respectively, compared to the 2 mg every 8 weeks arm. The results of PPS for Week 60 were consistent with those in the FAS.

Proportion of Patients Gaining ≥15 ETDRS Letters at Week 48

The between-group difference in the proportion of patients gaining 15 or more letters in BCVA from baseline to week 48 was -1.75% (95% CI, -7.78 to 4.29%; p = 0.5704) for aflibercept 8 mg every 12 weeks versus 2 mg every 8 weeks, and -0.94% (95% CI, -7.00 to 5.12%; p = 0.7611) for aflibercept 8 mg every 16 weeks versus 2 mg every 8 weeks, based on LOCF in the FAS. The observed findings were maintained at week 60.

Presence of IRF or SRF at Week 48

At week 48, 71.1% and 66.8% of patients in the aflibercept 8 mg every 12 weeks and aflibercept 8 mg every 16 weeks arms respectively had no retinal fluid (no IRF and no SRF) compared with 59.4% in the aflibercept 2 mg every 8 weeks. This resulted in a difference in the proportion of patients with no IRF and SRF in the central subfield of 11.72% (95% CI, 4.52 % to 18.92%, p = 0.0001) for 8 mg every 12 weeks versus 2 mg every 8 weeks and 7.45% (95% CI, 0.14% to 14.76%, p = 0.0051) 8 mg every 16 weeks versus 2 mg every 8 weeks, based on LOCF in the FAS. The observed findings were maintained at week 60.

Frequency of Injections

At week 48, 251 (79.4%) and 239 (76.6%) of completers in the aflibercept 8 mg every 12 weeks and 8 mg every 16 weeks arms maintained their randomized treatment interval. This resulted in mean numbers of active injections through week 48 of 6.1 and 5.2 in the aflibercept 8 mg every 12 weeks and 8 mg every 16 weeks arms, respectively, compared to 6.9 in the aflibercept 2 mg every 8 weeks arm. Treatment group difference (95% CI) between 2 mg every 8 weeks aflibercept 8 mg every 12 weeks and aflibercept 2 mg every 8 weeks was -0.9 [redacted] injections and the difference between aflibercept 2 mg every 8 weeks and aflibercept 8 mg every 16

weeks and aflibercept 2 mg every 8 week was -1.8 [redacted] injections. At week 60, the mean (SD) of number of injections were 8.8 ([redacted]), 7.1 ([redacted]), and 6.2 ([redacted]) for the aflibercept 2 mg every 8 weeks, 8 mg every 12 weeks and 8 mg every 16 week, respectively.

NEI VFQ-25

LS Mean (SE) changes from baseline were observed in all arms at week 48, ranging from 3.35 [redacted] in the aflibercept 8 mg Q16 arm to 4.22 [redacted] in the aflibercept 2 mg Q8 arm. The difference in the LS mean change from baseline using the MMRM in the FAS, were -0.72 [redacted] for 8 mg every 12 weeks vs. 2 mg every 8 weeks and -0.87 [redacted] for both 8 mg every 12 weeks and 8 mg every 16 weeks vs. 2 mg every 8 weeks. The results were consistent at week 60.

Harms Results

Patients in the trial reported at least one ocular TEAE with similar proportions across the treatment arms (45% in the aflibercept 2 mg every 8 weeks arm, 42.4% in the aflibercept 8 mg every 12 weeks, and 42.3% in the aflibercept 8 mg every 16 weeks). The most common ocular TEAEs in all treatment arms were reduced visual acuity (6.3% in the aflibercept 2 mg every 8 weeks arm, 3.9% in the aflibercept 8 mg every 12 weeks, and 5.9% in the aflibercept 8 mg every 16 weeks arm), cataract (3.9%, 4.8%, and 4.4 %), retinal haemorrhage (4.5%, 3.6%, 3.8%). The proportion of patients with non-ocular TEAE were 59.8%, 59.4%, 61.2% in the aflibercept 2 mg every 8 weeks, the aflibercept 8 mg every 12 weeks, and the aflibercept 8 mg every 16 weeks arms, respectively. At least one treatment-emergent SAE was reported in 1.2% of patients in the aflibercept 2 mg every 8 weeks arm, and 2.1% of patients in each of the aflibercept 8 mg every 12 weeks and every 16 weeks arms. Retinal hemorrhage and retinal detachment were the most common SAE in the treatment groups with same percentage (0.3%, 0.6%,0.6% in the aflibercept 2 mg every 8 weeks arm, aflibercept 8 mg every 12 weeks and aflibercept 8 mg every 16 weeks, respectively).

The proportion of patients who discontinued treatment due to an ocular TEAE was 0.6% in the aflibercept 2 mg every 8 weeks arm, and 1.2% in both the aflibercept 8 mg every 12 weeks and every 16 weeks arms. In the aflibercept 2 mg every 8 weeks arm, death events were reported for 1.5% of patients. In the aflibercept 8 mg every 12 weeks arm, death events were reported for 0.9% and 0.6% in the aflibercept 8 mg every 12 weeks arm and aflibercept 8 mg every 16 weeks arm respectively. In terms of notable harms, cataracts occurred in 3.9% of patients treated with aflibercept 2 mg every 8 weeks and 4.8% of patients treated with the aflibercept 8 mg every 12 weeks, and 4.4% patients treated with the aflibercept 8 mg every 16 weeks. The incidence of increased intraocular pressure was 2.7% in the aflibercept 2 mg every 8 weeks arm and 3.3% in the aflibercept 8 mg every 12 weeks arm, and 3.0% in the aflibercept 8 mg every 16 weeks arm. The percentage of patients experienced retinal pigment epithelium tear was 0.9% in the aflibercept 2 mg every 8 weeks arm, 1.8% in aflibercept 8 mg every 12 weeks arm, and 0.9 % in the aflibercept 8 mg every 16 weeks arm.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for aflibercept 8 mg every 12 weeks and every 16 weeks versus aflibercept 2 mg every 8 weeks.

Table 3: Summary of Findings for aflibercept 8 mg every 12 weeks and every 16 versus aflibercept 2 mg every 8 weeks for patients with treatment-naïve nAMD

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2 mg Q8	Aflibercept 8 mg Q12 or Q 16	Difference		
Visual acuity							
Change from baseline in BCVA, LS mean (SE) letters Follow-up: 48 weeks	Aflibercept 8 mg every 12 weeks: 671 (1 RCT)	NA	7.03	6.06 (0.77)	0.97 fewer (2.87 fewer to 0.92 more)	High	Aflibercept 8 mg every 12 weeks results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2 mg every 8 weeks.
	Aflibercept 8 mg every 16 weeks: 674 (1 RCT)	NA	7.03	5.89 (0.72)	1.14 fewer (2.97 fewer to 0.69 more)	High	Aflibercept 8 mg every 16 weeks results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2 mg every 8 weeks.
Proportion of patients gaining ≥15 letters in BCVA from baseline Follow-up: 48 weeks	Aflibercept 8 mg every 12 weeks: 671 (1 RCT)	NA	22.1 per 100	20.7 per 100	1.8 fewer per 100 (7.8 fewer to 4.3 more per 100)	Moderate[a,b]	Aflibercept 8 mg every 12 weeks likely results in little-to-no clinically important difference in the proportion of patients gaining ≥15 letters from baseline when compared with aflibercept 2 mg every 8 weeks.
	Aflibercept 8 mg every 16 weeks: 674 (1 RCT)	NA	22.1 per 100	21.7 per 100	0.9 fewer per 100 (7.0 fewer to 5.1 more per 100)	Moderate[a,b]	Aflibercept 8 mg every 16 weeks likely results in little-to-no clinically important difference in the proportion of patients gaining ≥15 letters from baseline when compared with aflibercept 2 mg every 8 weeks.
Proportion of patients with no IRF and no SRF							
Proportion of patients with no IRF and no SRF Follow-up: 48 weeks	Aflibercept 8 mg every 12 weeks: 671 (1 RCT)	NR	59.4 per 100	71.1 per 100	11.7 more per 100 (4.5 to 18.9 more per 100)	Moderate[b,c]	Aflibercept 8 mg every 12 weeks likely results in little-to-no clinically important difference in the proportion of patients without IRF and SRF when compared with aflibercept 2 mg every 8 weeks.
	Aflibercept 8 mg every 16 weeks: 674 (1 RCT)	NR	59.4 per 100	66.8 per 100	7.5 more per 100 (0.1 to 14.8 more per 100)	Moderate[b,c]	Aflibercept 8 mg every 16 weeks likely results in little-to-no clinically important difference in the proportion of patients without IRF and SRF when compared with aflibercept 2 mg every 8 weeks.
Vision-related QoL (NEI VFQ-25)							

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2 mg Q8	Aflibercept 8 mg Q12 or Q 16	Difference		
Change from Baseline in NEI VFQ-25 Total Score, LS mean (SE) Follow-up: 48 weeks	Aflibercept 8 mg every 12 weeks: 671 (1 RCT)	NA	4.22	3.50 [redacted]	0.72 less [redacted]	Moderate[a,d]	Aflibercept 8 mg every 12 weeks likely results in little-to-no clinically important difference in the change from baseline in vision-related QoL when compared with aflibercept 2 mg every 8 weeks.
	Aflibercept 8 mg every 16 weeks: 674 (1 RCT)	NA	4.22	3.35 [redacted]	0.87 less [redacted]	Moderate[a,d]	Aflibercept 8 mg every 16 weeks likely results in little-to-no clinically important difference in the change from baseline in vision-related QoL when compared with aflibercept 2 mg every 8 weeks.
Number of injections							
Number of injections, LS mean (95% CI) Follow-up: 48 weeks	Aflibercept 8 mg every 12 weeks: 625 (1 RCT)	NA	6.9	6.1 [redacted]	0.9 fewer (NR)	Low[a,e]	Aflibercept 8 mg every 12 weeks may result in little-to-no clinically important difference in the frequency of injections when compared with aflibercept 2 mg every 8 weeks.
	Aflibercept 8 mg every 16 weeks: 621 (1 RCT)	NA	6.9	5.2 [redacted]	1.8 fewer (NR)	Low[a,e]	Aflibercept 8mg q16 may result in a reduction in the frequency of injections when compared with aflibercept 2 mg every 8 weeks.
Ocular SAEs							
Proportion of patients with ocular SAEs Follow-up: 60 weeks	Aflibercept 8 mg every 12 weeks: 671 (1 RCT)	NR	1.2 per 100	2.1 per 100	0.9 more per 100 (NR)	Moderate[a,f]	Aflibercept 8 mg every 12 weeks likely results in little-to-no difference in the proportion of patients with ocular SAEs when compared with aflibercept 2 mg every 8 weeks. There may be some uncertainty about the clinical importance of the effect.
	Aflibercept 8mg every 16 weeks: 674 (1 RCT)	NR	1.2 per 100	2.1 per 100	0.9 more per 100 (NR)	Moderate[a,f]	Aflibercept 8 mg every 16 weeks likely results in little-to-no difference in the proportion of patients with ocular SAEs when compared with aflibercept 2 mg every 8 weeks. There may be some uncertainty about the clinical importance of the effect.

BCVA= best corrected visual acuity; CI = confidence interval; IRF= intraretinal fluid; NEI VFQ-25= National Eye Institute Visual Functioning Questionnaire-25; NR= not reported; SAEs= serious adverse events; QoL= quality of life; LS = least square;; RCT = randomized controlled trial SE= standard error; SRF= subretinal fluid; Q8 = every 8 weeks; Q12= every 12 weeks; Q16 = every 16 weeks

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] There was not a hypothesis test for this outcome in the trial; the result can be considered as supportive evidence.

[b] Rated down 1 level for serious concerns about risk of bias due to missing outcome data. Did not rate down for imprecision; a between-group difference of greater than 20% was clinically significant according to the clinical expert; the entire CI is compatible with little-to-no difference.

[c] There is no multiplicity adjustment; the result can be considered as supportive evidence.

[d] Rated down 1 level for serious concerns about risk of bias due to missing outcome data. Did not rate down for imprecision. Based on literature 6 point change from the baseline in NEI VFQ-25 total score was clinically important, the point estimate and entire confidence interval suggest little-to-no difference.

[e] Rated down 1 level for serious concerns about risk of bias due to missing outcome data. Did not rate down for imprecision; the clinical expert considered a difference of 2 injections in this timeframe to be clinically important; the sample size was adequately large. Rated down 1 level for serious indirectness because the number of injections was driven by the protocol and not reflective of how injections would be provided in practice.

[f] The clinical expert consulted by CADTH were unable to estimate a threshold for clinically important effects, so the null was used. Rated down 1 level for serious imprecision due to the small number of events.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis; Markov model
Target population	Adults with nAMD
Treatment	Aflibercept 8 mg, administered every 16 weeks (Q16w)[a]
Dose Regimen	8 mg administered by intravitreal injection every 4 weeks for first 3 doses, followed by 8 mg at a dosing interval of every 8 to 16 weeks
Submitted Price	Aflibercept 8 mg, 30 mg per 0.263 mL, single-use vial: $1,250.00
Treatment Cost	$6,250 to $10,000 in the first year, based on 5 to 8 injections. $5,000 to $8,750 in subsequent years, based on 4 to 7 injections.
Comparators	• Aflibercept 2 mg • Bevacizumab • Brolucizumab • Faricimab • Ranibizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (25 years)
Key data sources	• PULSAR trial to inform clinical efficacy of aflibercept 8 mg • Comparative clinical efficacy (change in BCVA) and administration frequency were informed by a sponsor-submitted ITC
Key limitations	• The comparative efficacy and safety of aflibercept 8 mg Q16w relative to other anti-VEGFs is uncertain owing to a lack of head-to-head trials and limitations with the sponsor's ITCs. Indirect evidence submitted by the sponsor suggests that there may be no meaningful difference in the efficacy or safety for aflibercept 8 mg compared to other currently available treatments for nAMD due to uncertainty in the ITC results. • The relative frequency of administration for aflibercept 8 mg and comparators is uncertain owing to limitations with the sponsor's submitted evidence for administration frequency and the individualized approach to administration frequency in clinical practice
CADTH reanalysis results	• There is insufficient clinical evidence to justify a price premium for aflibercept 8 mg relative to currently available treatments for nAMD.

BCVA = best corrected visual acuity; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; nAMD = neovascular age-related macular degeneration; QALY= quality-adjusted life-year; Q12 = every 12 weeks; Q16 = every 16 weeks.

[a] In the sponsor's base case, aflibercept 8 mg was assumed to be administered every 16 weeks. Administration of aflibercept 8 mg every 12 weeks was considered in scenario analysis.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the administration frequency for aflibercept 8 mg and other anti-VEGF inhibitors is uncertain; the number of administrations per vial for some comparators may be underestimated; the displacement of comparators by aflibercept 8 mg is uncertain; the price of drugs paid by the public drug plans is uncertain. In the absence of more reliable input values to estimate the key parameters of the BIA, the sponsor's base case was maintained. The sponsor's analysis estimates that reimbursing aflibercept 8 mg for the treatment of nAMD will be cost-saving for the public drug plans (3-year incremental budgetary savings of $158,158,913). CADTH explored uncertainty in this estimate via scenario analyses that

included adopting alternative assumptions about the administration frequency of anti-VEGF drugs, vial sharing, displacement of anti-VEGFs by aflibercept 8 mg, and the introduction of an aflibercept 2 mg biosimilar. Results of CADTH's scenario analyses suggest that the budget impact of reimbursing aflibercept 8 mg for nAMD is highly sensitive to administration frequency of anti-VEGFs, vial sharing, and the availability of an aflibercept 2 mg biosimilar. Results of these analyses ranged from a cost savings of $171 million to an incremental cost of $21.5 million over the first three years of reimbursement. As such, whether there is cost savings and the extent of any savings realized by the drug plans is highly uncertain.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

Meeting date: January 24, 2024

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None