CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Aflibercept (Eylea HD)
Indication: For the treatment of diabetic macular edema (DME)
Sponsor: Bayer Inc.

Recommendation: Reimburse with Conditions

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CADTH

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that aflibercept 8 mg/0.07 mL (aflibercept 8 mg) be reimbursed for the treatment of diabetic macular edema (DME) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase II/III, multicentre randomized, double-masked, active-controlled, non-inferiority trial PHOTON (N=660) demonstrated that treatment with aflibercept 8 mg every 12 weeks (Q12) or 16 weeks (Q16) was non-inferior in improving best-corrected visual acuity (BCVA) in patients with DME compared with aflibercept 2 mg administered every 8 weeks (Q8). Specifically, at week 48, treatment with aflibercept 8 mg Q12 and Q16 demonstrated non-inferiority to aflibercept 2 mg Q8 with between-group differences in LS mean changes from baseline of -0.57 letters (95% CI -2.26 to 1.13, non-inferiority P value <0.0001) for the aflibercept 8 mg Q12 and -1.44 letters (95%CI -3.27 to 0.39, non-inferiority P value 0.0031) for aflibercept 8 mg Q16 groups, compared with aflibercept 2 mg Q8. Similarly, at week 60, treatment with aflibercept 8 mg Q12 and Q16 demonstrated non-inferiority to aflibercept 2 mg Q8. The between-group differences in LS mean changes from baseline were -0.88 letters (95% CI -2.67 to 0.91, non-inferiority P value 0.0003) for the aflibercept 8 mg Q12 and -1.76 letters (95%CI -3.71 to 0.19, non-inferiority P value 0.0122) for aflibercept 8 mg Q16 compared to aflibercept 2 mg Q8. Evidence from PHOTON suggests that the longer intervals between dosing of aflibercept 8mg lead to less injections: at week 60, mean (standard deviation [SD]) numbers of injections were 7.0 (SD = [redacted]) with the aflibercept 8 mg Q12 and 6.0 (SD = [redacted]) for aflibercept 8 mg Q16 compared with 9.8 (SD = [redacted]) for aflibercept 2 mg Q8. In the absence of direct comparative evidence versus other currently available treatments for DME, a sponsor-submitted indirect treatment comparison (ITC) had insufficient evidence for a definitive conclusion about meaningful differences in safety and efficacy between aflibercept 8 mg and other currently available treatments for DME due to imprecision and unresolved heterogeneity. Also, the ITC analyzed the mean number of injections as an absolute outcome within each intervention node without comparisons across interventions, which made it difficult to access the comparative difference in the number of injections between aflibercept 8 mg and the comparator treatments.

CDEC concluded that aflibercept 8 mg Q12 and Q16 demonstrated similar clinical benefits compared with aflibercept 2 mg Q8 and may meet the need for less frequent injections, identified by patients and clinicians as an important outcome for the treatment of DME, although it was noted that the supporting evidence from the PHOTON trial was associated with low certainty because of the risk of bias due to missing data.

Due to limitations in the comparative efficacy evidence from the sponsor's 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 DME. Aflibercept 8 mg should not exceed the drug program cost with the least costly anti-VEGF reimbursed for the treatment of DME.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with all of the following: 1.1. Diabetes mellitus (type 1 or 2) 1.2. DME with central retinal thickness (CRT) ≥ 300 µm (or ≥ 320 µm on Spectralis) 1.3. Early treatment diabetic retinopathy study (ETDRS) letter score of 78 to 24 (approximate Snellen equivalent of 20/32 to 20/320) in the eye with decreased vision determined to be primarily the result of DME	Evidence from the pivotal PHOTON trial showed that treatment with aflibercept 8 mg resulted in BCVA benefits in patients with these characteristics.	Aflibercept 8 mg could be initiated in a similar manner to other anti-VEGF drugs for DME 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 the 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 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 DME in the absence of other pathology.	This is to ensure that aflibercept 8mg 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 DME as per the reimbursement criteria for each public drug plan.

Reimbursement condition	Reason	Implementation guidance
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 despite optimum treatment over 3 consecutive visits		
Prescribing		
5. The patient should be under the care of an ophthalmologist with experience in managing DME.	To ensure that the treatment is prescribed and administered safely for appropriate patients.	Aflibercept 8 mg could be prescribed in a similar manner to other anti-VEGF drugs for DME 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 PHOTON trial, aflibercept 8 mg at either every 12 weeks or 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 has 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 DME.	Results from a sponsor-submitted indirect treatment comparison (ITC) suggested no meaningful differences between aflibercept 8 mg and other currently available treatments for DME, although imprecision and unresolved heterogeneity precludes meaningful conclusions. As such, there is insufficient evidence to justify a cost premium for aflibercept 8 mg over the least expensive anti-VEGF reimbursed for DME.	—

BCVA: best corrected visual acuity; DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

Discussion Points

- A GRADE assessment of outcomes from the PHOTON trial showed a high certainty in the evidence indicating that aflibercept 8 mg administered every 12 or 16 weeks was non-inferior (but not superior) to aflibercept 2 mg every 8 weeks in improving BCVA scores over baseline after 48 weeks treatment. The non-inferiority benefit was maintained with high certainty at the week 60 assessment.

- CDEC noted that the PHOTON trial lacked direct safety and efficacy evidence for the comparison of aflibercept 8 mg versus other available treatments for DME, except aflibercept 2mg, noting that some newer anti-VEGF treatment for DME (e.g. faricimab) offer 12-week and/or 16-week injection intervals. The committee observed that the sponsor-submitted ITC had insufficient evidence to suggest that aflibercept administered at either 12-week or 16-week intervals was superior or

inferior to any of the other anti-VEGF treatments for DME. Hence, there was uncertainty regarding any safety and efficacy benefits if patients switched from another anti-VEGF to aflibercept 8 mg.

- CDEC discussed the importance of reduced injection frequency to both patients and clinicians because it has implications for treatment burden, and vision-related quality of life. The committee noted that a GRADE assessment found that the evidence supporting decreased injection frequency for aflibercept 8 mg compared to 2mg in the PHOTON trial was associated with low certainty because of serious concerns about the risk of bias due to missing data. CDEC also observed that the fixed injection interval regimen, used in both the PHOTON study and the sponsor-submitted ITC, does not align with the treat-and-extend strategy favoured in Canadian clinical practice. The committee determined that these are sources of uncertainty about whether the lower injecting frequency gains reported for aflibercept 8 mg are clinically meaningful, and if the gains would be replicated in settings using the treat-and-extend strategy.

- CDEC discussed the importance of glycemic control to achieving optimal treatment outcomes and noted that the PHOTON trial excluded patients with hemoglobin A1c (HbA1c) > 12%. However, the committee agreed with the clinical expert consulted that glycemic control targets may vary for individual patients, making a single A1c level an arbitrary criterion to select patients with DME who may be treated with the drug. The committee was of the view that glycemic control issues be left to the discretion of the treating ophthalmologist.

- 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 DME. CDEC recognized that drug plans may or may not consider bevacizumab a relevant comparator in their negotiations.

Background

Diabetic macular edema (DME) is the principal cause of vision impairment among people with diabetes, affecting the central region of the retina and leading to fluid accumulation and macular thickening. The multifactorial pathogenesis involves chronic hyperglycemia resulting in oxidative stress, retinal hypoxia, and increased levels of inflammatory cytokines like vascular endothelial growth factor (VEGF), which further compromise the integrity of the blood-retina barrier. This condition is prevalent among Canadian adults, with about 60,000 people experiencing DME-related vision loss. The highest rates are noted in the age group above 60 years and in Indigenous communities, contributing significantly to morbidity by decreasing quality of life and increasing the risk of mental health issues and social isolation.

Current diagnostic protocols for DME involve a series of retinal imaging and visual acuity assessments, with optical coherence tomography (OCT) being a cornerstone non-invasive imaging technique for detailed retinal evaluation. The primary therapeutic strategy consists of intravitreal anti-VEGF injections, which directly target the pathophysiological mechanisms underlying DME. These include aflibercept 2 mg, ranibizumab, brolucizumab, and faricimab. Bevacizumab is also an off-label treatment for this condition. Such therapies, recommended by several international ophthalmology societies, are vital in managing disease progression and improving visual outcomes. However, challenges such as frequent injections contribute to high treatment burden, highlighting the need for therapies that allow for extended treatment intervals. Safety concerns with these therapies include intraocular inflammation, necessitating a balance between efficacy and safety in patient care. The clinical expert noted that there are different treatment strategies currently in practice for the management of DME including a fixed dosing regimen, Pro Re Nata regimen/ as needed (PRN), and Treat and Extend regimen (T&E) where after initial treatment the duration between doses are extended as much as possible while maintaining treatment response goals.

Aflibercept, 8 mg is an anti-VEGF agent that received Health Canada notice of compliance (NOC) for the treatment of DME on February 2, 2024. It is administered as an intravitreal injection every month (4 weeks) for the first 3 consecutive doses and followed by 8 mg (0.07 mL) every 8 to 16 weeks (+/- 1 week) based on the physician's judgement of visual and anatomic outcomes. Treatment intervals of 1 month (4 weeks) for more than 3 consecutive doses have not been studied.

Aflibercept 2mg has previously been reviewed by CADTH for DME and macular edema secondary to central retinal vein occlusion and received a recommendation on May 7, 2015, to reimburse with conditions (i.e., aflibercept 2mg should be listed in a manner similar to ranibizumab and it should provide cost savings for drug plans relative to ranibizumab for the treatment of DME). On July 27, 2016, another recommendation to reimburse was issued by CADTH for the treatment of branch retinal vein occlusion (BRVO). Aflibercept 2mg is funded across CADTH-participating jurisdictions for DME.

Sources of Information Used by the Committee

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

- a review of 1 phase II/III, randomized, double-masked, active-controlled, non-inferiority trial in adult patients (≥18 years) with DME involving the centre of the macula.
- One sponsor-submitted indirect treatment comparison (ITC).
- Patients' perspectives gathered by patient groups (the Canadian Council of the Blind, a joint patient input from Fighting Blindness Canada (FBC), the Canadian Council of the Blind, Vision Loss Rehabilitation Canada, Diabetes Canada, and the International Federation on Ageing (IFA), and a commentary from the 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 DME involving the centre of the macula.
- Input from 6 clinician groups, including the Southwestern Ontario Community Ophthalmologists, Toronto Retina Institute, Northeastern Ontario Ophthalmology Group, Retina Division of the Ottawa Hospital, Toronto Ophthalmologists, and the Canadian Retina Society
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Input from the Canadian Council of the Blind, a joint patient input from Fighting Blindness Canada (FBC), the Canadian Council of the Blind, Vision Loss Rehabilitation Canada, Diabetes Canada, and the International Federation on Ageing (IFA) were summarized for this report. Overall, patients expressed that DME had substantial and life-altering impacts on their daily lives, and they worried about losing vision over time. Patients reported that they experienced significant emotional, psychological, and social issues. DME impacted how they completed daily tasks such as reading, using a phone, and driving, and they expressed needing help to get to appointments. Although most patients expressed satisfaction with their current treatment options, a significant number expressed anxiety or fear regarding treatments due to events that occurred post-injections. Some patients experienced notable visual complications such as scratchiness or pain in the eye following injections; others indicated that they were unable to complete at least one regular activity post-injection such as watch television, read, or drive and required assistance to carryout everyday tasks. Overall, patients across surveys expressed the need for treatments that reduce the impact of injections (e.g., pain) and the burden of repeated appointments as is the case with current treatments. In addition, patients living in rural communities and vulnerable populations experienced greater travel burdens (e.g., increased challenges attending appointments), contributing to missed appointments. Barriers to treatment access can potentially discourage patients from attending their appointments, resulting in vision worsening, and a consequent increase in healthcare expenditure, according to the patient groups. The patient groups highlighted current issues with the health care system such as surgery backlogs and the inability to overcome the backlog due to limited number of specialists. Therefore, any treatment that reduces physical, psychological, and logistical strain on patients and the healthcare system would be preferred, according to the groups.

Clinician Input

Input From Clinical Expert Consulted by CADTH

The clinical expert engaged by CADTH underscored the difficulties in managing DME due to the required frequent treatments which is burdensome for patients. The expert notes that the effects of most existing treatments typically do not last beyond 8 weeks, creating a significant inconvenience and hindering optimal outcomes. There is a demand for therapies that allow for longer intervals between treatments to reduce treatment burden, with newer anti-VEGF agents like faricimab and brolucizumab suggesting extended intervals of up to 12 or even 16 weeks, though the safety profile of these newer agents is not as well-known as the older agents. There remains an unmet need for a treatment that is both long-lasting and has an acceptable safety profile.

The expert also highlighted the potential for aflibercept 8mg to be used as a first-line treatment for DME or as an alternative when other treatments fail to provide control or pose too great a patient burden. Aflibercept 8mg is suitable for a wide range of DME patients, particularly those who are treatment-naive or have responded to prior anti-VEGF treatments but require a longer-lasting effect.

In clinical practice, visual acuity, and OCT measurements, alongside fundus examinations, are critical for monitoring treatment response. After an initial phase of monthly treatments, intervals may extend to 12 weeks and be adjusted based on patient response. Treatment discontinuation may be necessary if there is no improvement or worsening of the condition.

Prescribing aflibercept 8 mg should be done in a clinical setting by an ophthalmologist with expertise in retinal diseases.

Clinician Group Input

Input from 6 clinician groups, the Southwestern Ontario Community Ophthalmologists, Toronto Retina Institute, the Canadian Retina Society, Retina Division of the Ottawa Hospital, the Northeastern Ontario Ophthalmology Group, and the Toronto Ophthalmologists were summarized for this review. Treatment goals highlighted were consistent across inputs i.e., to maintain vision (i.e., stabilizing visual acuity and prevent worsening) and to improve quality of life, while extending the duration between treatments. The clinician groups highlighted that although current treatments target the underlying disease mechanism, they are not curative, and the extent and duration of damage to the retina may impact the ability to achieve improvement. Thus, there is an unmet need for efficacious and durable treatments that can reliably extend the treatment interval to minimize treatment burden for patients, caregivers, and the

health care system. The clinician groups also highlighted the need for safer treatments that minimize ocular complications owing to known safety concerns related to inflammation and occlusive retinal vasculitis observed with brolucizumab. According to the clinician groups, aflibercept 8 mg may become the drug of choice for treatment-naïve patients and they anticipate that it will replace aflibercept 2 mg formulation establishing it as a new first-line treatment choice for DME. Response to treatment will be assessed by assessing stabilization of vision and anatomical outcomes. Eye anatomy will be measured via optical coherence tomography (OCT) scans highlighted the clinician groups. According to the groups, factors that will impact any decisions to discontinue aflibercept 8 mg will be similar to the aflibercept 2 mg formulation (for example based on no response or the presence of irreversible macular damage). Treatment with aflibercept 8 mg will be primarily administered in the ophthalmologist's office, and rarely at hospital outpatient clinics according to the groups.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for aflibercept 8mg:

- Relevant comparators
- Consideration for initiation of therapy
- Consideration for discontinuation of therapy
- Consideration for prescribing of therapy
- System and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
The PHOTON study is a phase 3, multicenter, randomized, double-masked, active-controlled trial that assessed the effectiveness, safety, and tolerability of a higher dose of aflibercept (8mg) against the standard aflibercept (Eylea) 2mg dose. It aimed to evaluate whether two extended dosing regimens of aflibercept 8 mg were at least as effective as Eylea 2 mg. Notably, there were no comparative trials conducted between aflibercept 8mg and other extended-interval anti-VEGF medications like brolucizumab-dbll and faricimab.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for initiation of therapy	
Eligibility for disease diagnosis, scoring, or staging varies across provinces, with most having retinal programs in place. PHOTON trial inclusion criteria specify that patients must have diabetic macular edema (DME) with central involvement and central retinal thickness (CRT) of at least 300 micrometers—or 320 on Spectralis—confirmed by a reading center at the screening visit. Additionally, patients must have a best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score	This is a comment from the drug plans to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
ranging from 78 to 24, equivalent to a Snellen vision of 20/32 to 20/320, with vision loss attributed to DME.	
The initiation criteria for treatments in the same category as aflibercept 8mg have seen changes over time. The 2012 recommendation for ranibizumab included specific initiation criteria, such as the presence of clinically significant diabetic macular edema where laser photocoagulation is also indicated, and a hemoglobin A1c level below 11%. This recommendation, however, might be considered outdated, especially since it mandates an A1C level, a requirement that has since been removed by many jurisdictions. In contrast, the 2014 guidance for Eylea 2 mg suggested listing it in a manner akin to ranibizumab. Recommendations for brolucizumab and faricimab also advised listing them similarly to other anti-VEGF drugs. A question arises for CDEC and clinical experts: Are the 2012 ranibizumab criteria still relevant for the application to aflibercept 8mg in the treatment of DME? If they are no longer suitable, updated criteria are needed. For instance, could the criteria used for the PHOTON trial be more appropriate for current practice?	The clinical expert noted that the 2012 recommendation for ranibizumab is based on the eligibility of patients to undergo laser photocoagulation. Current practice and guidelines have changed, and patients no longer undergo laser photocoagulation at the same rate as they did in 2012. Furthermore, the clinical expert noted that glycemic control is important in achieving optimal therapeutic outcomes. However, glycemic control can be achieved in a reasonable period of time. CDEC noted the importance of glycemic control however the committee agreed with the clinical expert that A1c levels should not be a patient-selection criterion to initiate aflibercept 8 mg treatment for DME.
Considerations for discontinuation of therapy	
Should discontinuation criteria be included in the recommendation?	The clinical expert noted that a number of key considerations should be taken into account when considering discontinuation. These would include decreasing visual acuity, the persistent or increase intraretinal or subretinal fluid, or development of new subretinal hemorrhage despite active treatment. Typically, this assessment can take place after at least three injections. In such instances, it is important to consider either changing the treatment or stopping it altogether, given the lack of intended effects and the inherent risks associated with each injection. Additionally, for patients in the advanced stages of the disease who have substantial scarring, the benefits of anti-VEGF treatments are likely to be minimal, suggesting that treatment discontinuation should be considered. CDEC suggested that aflibercept 8mg be discontinued in a similar manner to other anti-VEGFs currently reimbursed for the treatment of adult patients with DME, such as having no response or the presence of irreversible macular damage.
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	This is a comment from the drug plans to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
weeks for the first 4 doses then every 8, 12 or 16 weeks.	
Does aflibercept 8 mg meet an unmet need given there are other products marketed with an extended dosing interval?	The clinical expert noted that aflibercept 8mg has an established option to extend to 16 weeks and comes with the added advantage of a known safety profile after over 10 years of clinical experience administering 2 mg aflibercept. CDEC noted that evidence from the PHOTON trial indicates that aflibercept 8 mg is non-inferior, but not superior to aflibercept 2 mg. Also, evidence from the sponsor-submitted ITC was insufficient to suggest that either aflibercept 8 mg Q12 or Q16 is clinically superior or inferior to any of the other anti-VEGF treatments currently reimbursed for the treatment of adult patients with DME. CDEC acknowledged that the extended dosing interval with aflibercept 8 mg provides an alternative to the extended interval options currently available. CDEC determined that the additional convenience with aflibercept 8 mg Q12 or Q16 may not justify additional cost, and there is lack of evidence to the clinical benefit of Q16W treatment against other anti-VGEFs.
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 2mg next year. Public drug plans have 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 2mg due to prescriber switching from ranibizumab to avoid the recently implemented brolucizumab biosimilar switch initiative. It is expected that this would occur with aflibercept 8mg. Question for CDEC: 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 DME.	Please refer to Table 1 for pricing condition.
Confidential pricing agreements exist for most anti-VEGF drugs.	This is a comment from the drug plans to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
Retinal programs/provincials eye centers exist in a number of provinces. Bevacizumab first policies in place in a number of provinces.	This is a comment from the drug plans to inform CDEC deliberations.

CDEC= CADTH Canadian Drug Expert Committee; DME = diabetic macular edema; VEGF= vascular endothelial growth factor.

Clinical Evidence

Systematic Review

Description of Studies

PHOTON (N=660) met the inclusion criteria for the systematic review conducted by the sponsor. PHOTON was a phase 3, active-controlled, non-inferiority, multinational (138 sites, including 4 sites in Canada) trial that randomized 660 patients with DME in a 1:2:1 ratio to either aflibercept 2 mg Q8, aflibercept 8 mg Q12, or aflibercept 8 mg q16w, respectively. The primary outcome was change from baseline in best-corrected visual acuity (BCVA) measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at week 48, and a key secondary outcome included change from baseline in BCVA measured by the ETDRS letter score at week 60. Other secondary and exploratory outcomes relevant to this review included proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in central subfield at week 48 and week 60, proportion of participants gaining at least 15 letters in BCVA from baseline at week 48 and 60, and vision-related quality of life at week 48 and 60. Total number of injections, treatment emergent adverse events (TEAEs), and serious adverse events (SAEs) through week 60 were reported under harms.

The treatment arms were generally well balanced with respect to baseline disease and demographic characteristics. Patients were numerically similar in age, with a slightly younger average in the aflibercept 8 mg Q16 group (mean 61.9 years, SD 9.50) contrasted to the aflibercept 2 mg Q8 (mean 63.0 years, SD 9.78). There was a numerically higher proportion of male patients in the higher dosage aflibercept groups (aflibercept 8 mg Q12 [64.0%] and aflibercept 8 mg Q16 [60.7%] groups contrasted to the aflibercept 2 mg Q8 group [55.1%]). The majority of patients were white, with a numerically higher proportion in the aflibercept 8 mg Q16 group (78.5%) contrasted to the aflibercept 2 mg Q8 group (67.1%). The mean duration of diabetes was numerically similar across groups, and the majority had type II diabetes. Ocular characteristics like BCVA and central retinal thickness (CRT) were similar across groups, with marginal variations in BCVA and CRT means among the different dosage groups.

Efficacy Results

Change from Baseline in BCVA at Week 48

The change from baseline in BCVA at week 48 was the primary non-inferiority endpoint in PHOTON. The primary endpoint was met: treatment with aflibercept 8 mg Q12 and Q16 demonstrated non-inferiority to aflibercept 2 mg Q8 using a non-inferiority margin of 4 letters. The LS mean changes in BCVA from baseline to week 48 were 8.1 letters (SE = 0.61) and 7.2 letters (SE = 0.71) for the aflibercept 8 mg Q12 and Q16 arms, respectively, compared with 8.7 letters (SE = 0.73) in the aflibercept 2 mg Q8 arm. Between-group differences in LS mean changes from baseline were -0.57 letters (95% CI -2.26 to 1.13, non-inferiority P value <0.0001) and -1.44 letters (95%CI -3.27 to 0.39, non-inferiority P value 0.0031) for the aflibercept 8 mg Q12 and aflibercept 8 mg Q16 arms, respectively, compared with the aflibercept 2 mg Q8 arm. The supplementary per protocol analysis was consistent with the main analysis.

Change from Baseline in BCVA at Week 60

The corresponding key secondary endpoint of change from baseline in BCVA at week 60 was met: treatment with aflibercept 8 mg Q12 and aflibercept 8 mg Q16 demonstrated non-inferiority to aflibercept 2 mg Q8 using a non-inferiority margin of 4 letters, with LS mean changes from baseline BCVA to week 60 of 8.5 letters (SE = 0.63) and 7.6 letters (SE = 0.75), respectively, compared with 9.4 (SE = 0.77) letters in the aflibercept 2 mg Q8 arm. Between-group differences in LS mean changes from baseline were -0.88 letters (95% CI -2.67 to 0.91, non-inferiority P value 0.0003) and -1.76 letters (95%CI -3.71 to 0.19, non-inferiority P value 0.0122) letters for the aflibercept 8 mg Q12 and aflibercept 8 mg Q16 groups, respectively, compared to the aflibercept 2 mg Q8 group.

Proportion of Patients Gaining ≥15 ETDRS Letters at Week 60

At Week 60, in the aflibercept 2 mg Q8 group, 43 out of 165 patients (26.1%) gained at least 15 letters in BCVA from baseline. For the aflibercept 8 mg Q12 group, 70 out of 326 patients (21.5%) showed at least a 15-letter gain. In the aflibercept 8 mg Q16 group, 26 out of 163 patients (16.0%) recorded such gains. When comparing to the aflibercept 2 mg Q8 group, the differences in proportions of patients achieving at least a 15-letter gain for the aflibercept groups were -5.01% (95% CI -13.04 to 3.02) for the Q12 group and -10.78% (95% CI -19.27 to -2.29) for the Q16 group. This was an exploratory endpoint.

Proportion of Patients with BCVA ≥ 69 letters at Week 60

At Week 60, in the aflibercept 2 mg Q8 group, 100 out of 165 patients (60.6%) had a BCVA ≥ 69 ETDRS letters. For the aflibercept 8 mg Q12 group, 211 out of 326 patients (64.7%) had a BCVA ≥ 69 ETDRS letters. In the aflibercept 8 mg Q16 group, 101 out of 163 patients (62.0%) recorded such scores. When comparing to the aflibercept 2 mg Q8 group, the differences in proportions of patients with BCVA ≥ 69 letters at Week 60 for the aflibercept groups were 4.34% (95% CI -4.27 to 13.40) for the Q12 group and 1.63% (95% CI -8.91 to 12.17) for the Q16 group. This was an exploratory endpoint.

Proportion of patients without fluid at foveal center at Week 60

Concerning the proportion of patients without fluid at the foveal center (no IRF and no SRF) at week 60, 68.5% (113 out of 165) from the aflibercept 2 mg Q8 group showed no fluid. In contrast, the aflibercept 8 mg Q12 group had 61.8% (201 out of 325) without fluid, with a difference of -5.98% [redacted]. For the Aflibercept 8 mg Q16 group, 58.0% (94 out of 162) were without fluid, resulting in a difference of -9.88 [redacted] from the aflibercept group. This was an exploratory endpoint.

Frequency of Injections at Week 60

At week 60, 90.3% of 289 patients and 85.5% of 152 patients who completed Week 60 in the in the aflibercept 8 mg Q12 and Q16 arms, respectively, maintained their randomized treatment interval. This resulted in mean numbers of active injections through week 60 of 7.0 (SD = [redacted]) and 6.0 (SD = [redacted]) in the aflibercept 8 mg Q12 and Q16 arms respectively, compared with 9.8 (SD = [redacted]) in the aflibercept 2 mg Q8 arm. Comparative differences were not reported.

NEI VFQ-25 at Week 60

At week 60, the LS mean (SE) increases in = National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) scores were 4.55 (SE = [redacted]) and 3.21 (SE = [redacted]) for aflibercept 8 mg Q12 and Q16, respectively, compared to 3.05 (SE = [redacted]) in the aflibercept 2 mg Q8 arm. Between-group differences in LS mean changes from baseline were 1.50 points (95%CI [redacted]) and 0.17 points (95%CI [redacted]) letters for the aflibercept 8 mg Q12 and aflibercept 8 mg Q16 groups, respectively, compared to the aflibercept 2 mg Q8 group.

Harms Results

Ocular treatment-emergent adverse events were reported in less than half of the enrolled patients. Specifically, 43.7% of patients (73 patients out of 167) in the aflibercept 2 mg Q8 group experienced at least one ocular TEAE. This percentage was 44.8% (or 147 out of 328 patients) in the aflibercept 8 mg Q12 group and the same percentage (44.8%, 73 out of 163 patients) for the aflibercept 8 mg Q16 group. At least one ocular treatment-emergent SAE was reported 0.6% of patients in the aflibercept 2 mg Q8 group (1 out of 167 patients), 0.6% in the aflibercept 8 mg Q12 group (2 out of 328 patients), and 1.2% in the aflibercept 8 mg Q16 group (2 out of 163 patients). Specific events under this category included conditions such as cataract subcapsular, retinal detachment (1 patient in the aflibercept 8 mg Q12 group), ulcerative keratitis (1 patient in aflibercept 2 mg Q8), and vitreous hemorrhage (1 patient in aflibercept 8 mg Q16).

Non-ocular serious adverse events were experienced by 19.2% of patients in the aflibercept 2 mg Q8 group (32 out of 167 patients), 18.6% in the aflibercept 8 mg Q12 group (61 out of 328 patients), and 16.6% in the aflibercept 8 mg Q16 group (27 out of 163 patients).

Of adverse events of special interest, in the aflibercept 2 mg Q8 group, 0.6% (1 out of 167 patients) of the participants experienced intraocular inflammation, while 3.6% (6 out of 167 patients) had increased intraocular pressure (IOP), and 3.6% (6 out of 167 patients) underwent an Anti-Platelet Trialists' Collaboration (APTC) event. In the aflibercept 8 mg Q12 regimen, 1.2% of the patients (4 out of 328 patients) presented with intraocular inflammation, 2.1% reported an increased IOP (7 out of 328 patients), and 4.0% (13 out of 328 patients) experienced an APTC event. Meanwhile, in the aflibercept 8 mg Q16 group, intraocular inflammation was observed in 0.6% of patients (1 out of 163 patients), 0.6% had an increase in IOP (1 out of 163 patients), and 5.5% had an APTC event (9 out of 163 patients). No cases of endophthalmitis or retinal vasculitis were reported in any of the treatment groups.

In the aflibercept 2 mg Q8 group, 3.0% of patients (5 out of 167 patients) died. Specific causes of death in this group included cardiac arrest (1.2%), myocardial infarction (0.6%), diabetic metabolic decompensation (0.6%), and acute kidney injury (0.6%). In the aflibercept 8 mg Q12 group, 2.7% of patients (9 out of 328 patients) had died. Specific causes of death in this group included cardiac arrest (0.6%), myocardial infarction (0.3%), COVID-19 (0.3%), pneumonia (0.3%), endometrial cancer (0.3%), and unknown (0.6%). In the aflibercept 8 mg Q16 group, 2.5% of patients (4 out of 163 patients) had a fatality. Specific causes of death in this group included cardiac-respiratory arrest (0.6%), myocardial infarction (0.6%), left ventricular failure (0.6%), and sudden death (0.6%).

Critical Appraisal

The overall design of PHOTON was appropriate for the objectives of the study. Randomization was stratified by baseline Best Corrected Visual Acuity (BCVA) and geographic region, utilizing an interactive response system to maintain allocation concealment. Baseline demographic and disease characteristics and concurrent treatments were mostly evenly distributed across the treatment groups. Notable imbalances in the baseline characteristics included a numerically higher proportion of male patients and higher proportion of White in the higher dosage aflibercept groups contrasted to the aflibercept 2 mg Q8 group. Statistical analytical approaches were similarly appropriate. Statistical analyses, including subgroup analyses, were predefined in the study protocol and the Statistical Analysis Plan (SAP). A hierarchical testing procedure was applied to primary and key secondary endpoints to control for type I error, though no such adjustment was included for Week 60 outcomes. The noninferiority margin was set at 4 ETDRS letters, supported by evidence and expert consultation. Both the Full Analysis Set (FAS) and Per-Protocol Set (PPS) analyses indicated noninferiority of the aflibercept 8 mg given at 12 weeks or 16 weeks intervals. Missing data in primary and key secondary outcomes was addressed using Mixed-Model Repeated Measures (MMRM) with sensitivity analyses employing Last Observation Carried Forward (LOCF) and other models assuming different missing data mechanisms, which corroborated the primary analysis results. In exploratory outcomes, missing data were handled through LOCF with observed cases sensitivity analysis or no sensitivity analysis. This may increase the risk of bias due to missing data in exploratory outcomes. Adjustments for type I error were accounted for in the primary and key secondary endpoints through a hierarchical testing procedure. However, no such adjustment was made for outcomes at Week 60, which are of high clinical value. This increases the possibility of type I error in statistically significant Week 60 endpoints.

The PHOTON trial included four sites in Canada. The inclusion and exclusion criteria as well as the patients baseline characteristics were representative of Canadian patients. In addition, outcomes reported in the trial are clinically important outcome and commonly utilized in Canadian clinical practice. Nonetheless, the trial's dosing regimen of aflibercept 2 mg at Q8W does not correspond with the regimen practiced in Canadian clinics, which follows a treat and extend protocol. This discrepancy raises questions about the generalizability of the study results, particularly the frequency of injections.

There is no evidence to support the efficacy and safety of switching, and no direct evidence to inform on the comparative efficacy and safety of aflibercept 8 mg versus other anti-VEGF therapies.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor’s Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The outcomes were finalized in consultation with expert committee members.

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

Table 3: Summary of Findings for aflibercept 8mg q12 and q16 versus aflibercept 2mg q8 for Patients With DME

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2mg q8	Aflibercept 8mg q12 or q16	Difference		
Change from baseline in BCVA							
Change from baseline in BCVA, LS mean (SE) letters Follow-up: 48 weeks (0 [worst] to 100 [best])	Aflibercept 8mg Q12: 328 (1 RCT)	NA	8.7	8.1 (0.61)	0.57 fewer letters (2.26 fewer to 1.13 more)	High[a]	Aflibercept 8mg Q12 results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2mg Q8.
	Aflibercept 8mg Q16: 163 (1 RCT)	NA	8.7	7.2 (0.71)	1.44 fewer letters (3.27 fewer to 0.39 more)	High[a]	Aflibercept 8mg Q16 results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2mg Q8.
Change from baseline in BCVA, LS mean (SE) letters Follow-up: 60 weeks (0 [worst] to 100 [best])	Aflibercept 8mg Q12: 328 (1 RCT)	NA	9.4	8.5 (0.63)	0.88 fewer letters (2.67 fewer to 0.91 more)	High[a]	Aflibercept 8mg Q12 results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2mg Q8.
	Aflibercept 8mg Q16: 163 (1 RCT)	NA	9.4	7.6 (0.75)	1.76 fewer letters (3.71 fewer to 0.19 more)	High[a]	Aflibercept 8mg Q16 results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2mg Q8.
Proportion of patients without fluid at foveal center*							
Proportion of patients without fluid at foveal center Follow-up: 60 weeks	Aflibercept 8mg Q12: 328 (1 RCT)	0.90 [redacted]	68.5 per 100	61.8 per 100 (NR)	5.98 fewer per 100 [redacted]	Moderate[b]	Aflibercept 8mg Q12 likely result in a decrease in the proportion of patients without fluid at the foveal centre when compared with aflibercept 2mg Q8. The clinical importance of the decrease is uncertain.
	Aflibercept 8mg Q16: 163 (1 RCT)	0.85 [redacted]	68.5 per 100	58.0 per 100 (NR)	9.88 fewer per 100 [redacted]	Moderate[b]	Aflibercept 8mg Q16 likely result in a decrease in the proportion of patients without fluid at the foveal centre when compared with aflibercept 2mg Q8. The clinical importance of the decrease is uncertain.
Proportion of patients with ETDRS letters gain*							

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2mg q8	Aflibercept 8mg q12 or q16	Difference		
Proportion of patients gaining ≥15 letters in BCVA from baseline Follow-up: 60 weeks	Aflibercept 8mg Q12: 328 (1 RCT)	0.82 [redacted]	26.1 per 100	21.5 per 100 (NR)	5.01 fewer per 100 (13.04 fewer to 3.02 more per 100)	Moderate[b]	Aflibercept 8mg Q12 likely result in a decrease in the proportion of patients gaining ≥15 letters from baseline when compared with aflibercept 2mg Q8. The clinical importance of the decrease is uncertain.
	Aflibercept 8mg Q16: 163 (1 RCT)	0.61 [redacted]	26.1 per 100	16.0 per 100 (NR)	10.78 fewer per 100 (19.27 fewer to 2.29 fewer per 100)	High[c]	Aflibercept 8mg Q16 results in a decrease in the proportion of patients gaining ≥15 letters from baseline when compared with aflibercept 2mg Q8. The clinical importance of the decrease is uncertain.
Proportion of patients with BCVA ≥ 69 letters Follow-up: 60 weeks	Aflibercept 8mg Q12: 328 (1 RCT)	1.07 [redacted]	60.6 per 100	64.7 per 100 (NR)	4.34 more per 100 (4.27 fewer to 13.40 more per 100)	Moderate[b]	Aflibercept 8mg Q12 likely result in an increase in the proportion of patients with ≥69 letters when compared with aflibercept 2mg Q8. The clinical importance of the increase is uncertain.
	Aflibercept 8mg Q16: 163 (1 RCT)	1.02 [redacted]	60.6 per 100	62.0 per 100 (NR)	1.63 more per 100 (8.91 fewer to 12.17 more per 100)	Low[d]	Aflibercept 8mg Q16 may result in an increase in the proportion of patients with ≥69 letters when compared with aflibercept 2mg Q8.
Vision-related QoL (NEI VFQ-25)*							
Change from Baseline in NEI VFQ-25 Total Score, LS mean (SE) points Follow-up: 60 weeks (0 [worst] to 100 [best])	Aflibercept 8mg q12: 328 (1 RCT)	NA	3.05	4.55 [redacted]	1.50 more points ([redacted])	High[e]	Aflibercept 8mg q12 results in little-to-no clinically important difference in the change from baseline in vision-related QoL when compared with aflibercept 2mg q8.
	Aflibercept 8mg q16: 163 (1 RCT)	NA	3.05	3.21 [redacted]	0.17 more points [redacted]	High[e]	Aflibercept 8mg q16 results in little-to-no clinically important difference in the change from baseline in vision-related QoL when compared with aflibercept 2mg q8.
Number of active injections*							

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2mg q8	Aflibercept 8mg q12 or q16	Difference		
Number of active injections, LS mean (95% CI) Follow-up: 60 weeks	Aflibercept 8mg q12: 289 (1 RCT)	NA	9.8	7.0 ([redacted])	2.8 fewer injections ([redacted])	Low [f]	Aflibercept 8mg Q12 likely results in a decrease in the frequency of injections when compared with aflibercept 2mg q8. The clinical importance of the decrease is uncertain.
	Aflibercept 8mg q16: 152 (1 RCT)	NA	9.8	6.0 ([redacted])	3.8 fewer injections ([redacted])	Low[f]	Aflibercept 8mg Q16 likely results in a decrease in the frequency of injections when compared with aflibercept 2mg q8. The clinical importance of the decrease is uncertain.
Ocular Serious Adverse Events (SAEs)							
Proportion of patients with ocular SAEs Follow-up: 60 weeks	Aflibercept 8mg q12: 328 (1 RCT)	NR	0.6 per 100	0.6 per 100 (NR)	NR	Low[g]	Aflibercept 8mg Q12 may have similar proportion of patients with ocular SAEs when compared with aflibercept 2mg q8.
	Aflibercept 8mg q16: 163 (1 RCT)	NR	0.6 per 100	0.6 per 100 (NR)	NR	Low[g]	Aflibercept 8mg Q16 may have similar proportion of patients with ocular SAEs when compared with aflibercept 2mg q8.

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.

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] Did not rate down for imprecision. The threshold for a clinically important difference was considered to be 4 letters (i.e., the non-inferiority margin); the point estimate and entire confidence interval suggest little-to-no difference.

[b] No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. Rated down 1 level down for serious imprecision as the lower bound of the CI suggests harm and the upper bound of the 95% CI suggests benefit and/or little to no difference.

[c] No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. Did not rate down for imprecision; a between-group difference of less than the null and a confidence interval that excludes the null suggest harm compared to aflibercept 2 mg Q8.

[d] No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. Rated down 2 level down for very serious imprecision as CI is very wide and contain potential for considerable harm in the lower bound of the CI and the upper bound may suggest considerable benefit.

[e] Did not rate down for imprecision. Based on literature 6.13-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.

[f] Rated down 1 level for serious concerns about risk of bias due to missing outcome data. 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. Did not rate down for imprecision; No published between-group MID was identified, and the clinical experts consulted by CADTH were unable to estimate a threshold for clinically important effects, therefore the null was used. The point estimate, the lower bound and the upper bound suggest benefit.

[g] Rated down 2 levels for very serious concerns about imprecision due to very small number of events.

* Not part of pre-defined statistical testing in the trial.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

Description of Studies

The Sponsor-submitted ITC used a Bayesian network meta-analysis (NMA) approach, under fixed-effect and random effects models, to compare aflibercept 8 mg Q12W and Q16W in patients with DME against other anti-VEGF agents used for this condition. The following outcome measures are reported here: change in BCVA, gain of 15 ETDRS letters, ocular adverse events, and the mean number of injections. The sponsor-submitted NMA identified relevant evidence through a systematic review approach. Depending on the outcome type, different statistical models and links were applied, including normal likelihood with an identity link for BCVA changes, binomial likelihood with a logit link for adverse events, and multinomial likelihood with a probit link for letter gains. Methodological and clinical heterogeneity was evaluated using study and patient characteristics, with statistical heterogeneity measured by I^2 statistics, and network inconsistency was assessed via node-splitting methods. The mean number of injections was analyzed as an absolute outcome within each intervention node but not comparatively across interventions. Missing data were imputed from external sources, and continuous and binary model inputs were adjusted for standard errors derived from various statistical distributions.

Efficacy Results

A total of 17 studies were included in the NMA one assessed aflibercept 8 mg, 11 assessed aflibercept 2 mg, six assessed ranibizumab, two assessed faricimab, nine assessed laser PRN, two assessed brolucizumab, and two assessed bevacizumab. Risk of bias assessment of the included studies in the sponsor ITC determined that 2 studies were of “high risk” as determined by the Cochrane risk of bias 2.0 tool. The sponsor ITC did not report any specific actions taken with the studies that were determined as having “High risk” of bias (e.g., sensitivity analyses).

Results from the majority of comparative outcomes under the random effects model did not exclude the null in the credible intervals, and the point estimates were, similarly, around the null. Notable exceptions include favorable results in letters gained for aflibercept 2 mg q4w when compared to aflibercept 8 mg, and favorable results for aflibercept 8 mg when compared to laser in the outcome of BCVA. In the outcome of letters gained, aflibercept 8 mg Q12 showed an unfavourable response against aflibercept 2 mg Q4 [redacted] and a favourable response against Laser [redacted] Aflibercept 8 mg Q16 showed an unfavourable response against aflibercept 2 mg Q8 [redacted] and against aflibercept 2 mg Q4 [redacted] and shows a favorable OR versus laser [redacted]

Based on pre-determined injections regimens, certain interventions are expected to have an average number of injections observed for each treatment regimen and tend to be consistent with the number of injections planned. Interventions administered on a fixed schedule did not show much variability between the planned and the actual number of injections given. Treat and extend and pro re nata regimens are not pre-determined and show a mean number of injections between 7.41 to 9.18 across the interventions in the first year and mean number of injections between 3.79 to 5.80 across the interventions in the second year. Absolute non-comparative results of injection frequency suggest that aflibercept 8 mg Q12 has a mean injection frequency of 6.00 in the first year, and 3.50 in the second year, while Q16W has a mean injection frequency of 5.00 in the first year, and 2.80 in the second year.

Harms Results

The relative effect of treatments on the number of ocular adverse events did not exclude the null in any of the credible intervals, except for the serious ocular adverse event comparison against bevacizumab, which shows favourable results to aflibercept 8 mg. For other comparisons, the 95% CrIs were wide, suggesting that either treatment could be favoured. No other safety endpoint was reported.

Critical Appraisal

The systematic literature review supporting the sponsor-submitted indirect treatment comparison (ITC) for aflibercept 8 mg in DME followed an acceptable systematic review approach. The review process was adequate for reducing the risk of bias and error in study selection and risk of bias appraisal. Two high risks of bias studies were identified; however, the authors did not conduct any analyses (e.g., sensitivity analyses) to investigate the impact of these studies on the results. Clinically relevant outcomes were measured, but the fixed injection regimens in the majority of included studies reduces the applicability of the findings to Canadian clinical settings, which favors treat-and-extend regimens. Despite appropriate Bayesian network meta-analysis methods, the clinical heterogeneity observed in the study populations — evidenced by variations in age, baseline visual acuity, glycemic control, and treatment history — raises concerns about the homogeneity assumptions of the NMA models. The sponsor's statistical testing for heterogeneity identified a number of heterogenous comparisons within the network. In addition, given that many treatment effects were supported by single-trial evidence, study and baseline characteristics variability increase the possibility of bias due to effect modifiers (e.g., disease duration, baseline disease severity, etc.), The absence of comparative data for injection frequency limits the interpretability of aflibercept 8 mg's potential benefits in reduction of injection frequency versus other interventions and regimens.

Studies Addressing Gaps in the Evidence from the Systematic Review

No studies addressing gaps in the systematic review evidence were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis; Markov model
Target population	Adults with DME
Treatment	Aflibercept 8 mg, administered every 16 weeks (Q16w)[a]
Dose Regimen	8 mg administered by intravitreal injection every 4 weeks for the 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 (38 years)
Key data sources	• PHOTON 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 NMA. 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 DME 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

Component	Description
CADTH reanalysis results	• There is insufficient clinical evidence to justify a price premium for aflibercept 8 mg relative to currently available treatments for DME.

BCVA = best corrected visual acuity; DME =diabetic macular edema; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; 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: administration 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 DME will be cost-saving for the public drug plans (3-year incremental budgetary savings of $46,404,196). 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 DME 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 $49.5 to an incremental cost of $10.3 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 25, 2024

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None