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CADTH Reimbursement Recommendation

Aflibercept 8 mg/0.07 mL (Eylea HD)

Indication: For the treatment of diabetic macular edema
Sponsor: Bayer Inc.
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for EYLEA HD?

CADTH recommends that aflibercept 8mg/0.07 mL (Eylea HD) be reimbursed by public drug plans for treating diabetic macular edema (DME) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Eylea HD should only be covered to treat adult patients with DME due to type 1 or 2 diabetes mellitus, with a central retinal thickness (CRT) of 300 µm or more (or 320 µm or more on the Spectralis scan) and a score of 78 to 24 letters in the eye with decreased vision primarily due to DME according to the early treatment diabetic retinopathy study (ETDRS) scoring system.

What Are the Conditions for Reimbursement?

Eylea HD should only be reimbursed if it is prescribed by an ophthalmologist with experience managing DME, it is used in combination with other antivascular endothelial growth factor (VEGF) drugs, and the cost of Eylea HD is not more than the least costly anti-VEGF drug covered by the public drug plans for the treatment of DME. Eylea HD should only be authorized for reimbursement for 12 months the first time it is used. Eylea HD should no longer be reimbursed if injections need to be given more frequently than every 12 weeks or if the patient experiences > 10 letter loss in best-corrected visual acuity (BCVA) from week 12 in association with persistent or worsening DME and > 50 µm increase in CRT from week 12.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial (the PHOTON trial) demonstrated that in patients with DME, the clinical benefits of Eylea HD injections at intervals of either every 12 weeks or 16 weeks is no worse (but no better) than aflibercept 2 mg/ 0.05 mL (Eylea) administered every 8 weeks.
- Based on CADTH's assessment of the health economic evidence, Eylea HD does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Eylea HD when compared with other anti-VEGF drugs covered by the public drug plans for patients with DME.
- Based on public list prices, Eylea HD may decrease costs for public drug plans; however, the extent of any savings realized will depend on the frequency of injection.

Summary

Additional Information

What Is DME?

DME is an eye disease that can occur in people living with diabetes. It is caused by blood vessels leaking fluid into a part of the eye called the macula, responsible for sharp central vision and fine detail. Untreated DME is a leading cause of visual loss, visual disability, and legal blindness in people with diabetes. It is estimated that 60,000 adults with DME in Canada experience vision impairment requiring treatment.

Unmet Needs in DME

Patients with DME expressed a need for new treatments that are effective, safe, and require fewer injections.

How Much Does DME Cost?

Treatment with Eylea HD is expected to cost between $6,250 and $10,000 per patient in the first year of use, depending on how many injections are required (between 5 and 8 injections). In subsequent years, the annual cost per patient is expected to be between $5,000 and $8,750 (based on 4 to 7 injections per year).

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 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, noninferiority PHOTON trial (N = 660) demonstrated that treatment with aflibercept 8 mg every 12 weeks (q12w) or 16 weeks (q16w) was noninferior in improving BCVA in patients with DME compared with aflibercept 2 mg administered every 8 weeks (q8w). Specifically, at week 48, treatment with aflibercept 8 mg q12w and q16w demonstrated noninferiority to aflibercept 2 mg q8w with between-group differences in least squares (LS) mean changes from baseline of −0.57 letters (95% confidence interval [CI], −2.26 to 1.13, noninferiority P value < 0.0001) for the aflibercept 8 mg q12w and −1.44 letters (95% CI, −3.27 to 0.39, noninferiority P value 0.0031) for aflibercept 8 mg q16 groups, compared with aflibercept 2 mg q8w. Similarly, at week 60, treatment with aflibercept 8 mg q12w and q16w demonstrated noninferiority to aflibercept 2 mg q8w. The between-group differences in LS mean changes from baseline were −0.88 letters (95% CI, −2.67 to 0.91, noninferiority P value 0.0003) for the aflibercept 8 mg q12w and −1.76 letters (95% CI, −3.71 to 0.19, noninferiority P value 0.0122) for aflibercept 8 mg q16 compared to aflibercept 2 mg q8w. Evidence from the PHOTON trial suggests that the longer intervals between dosing of aflibercept 8mg lead to fewer injections: at week 60, mean (standard deviation [SD]) numbers of injections were 7.0 (SD = [redacted]) with the aflibercept 8 mg q12w and 6.0 (SD = [redacted]) for aflibercept 8 mg q16w compared with 9.8 (SD = [redacted]) for aflibercept 2 mg q8w. 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 q12w and q16w demonstrated similar clinical benefits compared with aflibercept 2 mg q8w and may meet the need for less frequent injections, which patients and clinicians identified as an important outcome for treating DME. However, 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 impossible 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. Therefore, Aflibercept 8 mg should be negotiated

to not exceed the drug program cost, and the least costly comparator should be 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 similarly 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 12 months.	This is to help ensure that aflibercept 8 mg is used in patients who benefit from the treatment.	–
Discontinuation		
3. Aflibercept 8 mg should be discontinued upon any of the following: 3.1. Unable to be maintained on a 12-week or greater interval between injections based on the physician's judgment of visual and anatomic outcomes, Or 3.2. If a patient met these 2 conditions 3.2.1. > 10 letter loss in BCVA from week 12 in association with persistent or worsening DME and 3.2.2. > 50 µm increase in CRT from week 12.	This ensures that aflibercept 8mg is used in patients who benefit from treatment. Patients and clinicians expressed a need for drugs that have longer treatment intervals and thus require fewer injections. Patients in the aflibercept 8mg q12w weeks and q16w weeks arms of the PHOTON trial qualified for DRM (i.e., to receive injections at 8-week intervals as rescue regimen) at the beginning of week 16 if they had > 10 letter loss in BCVA from week 12 in association with persistent or worsening DME and > 50 µm increase in CRT from week 12.	Aflibercept 8 mg could be discontinued similarly to other anti-VEGF drugs for DME as per the reimbursement criteria for each public drug plan.

Reimbursement condition	Reason	Implementation guidance
Prescribing		
4. 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 similarly to other anti-VEGF drugs for DME as per the reimbursement criteria for each public drug plan.
5. Aflibercept 8 mg should not be prescribed in combination with other anti-VEGF drugs.	There was no submitted evidence to support the combination use of anti-VEGF drugs.	—
Pricing		
6. 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 preclude meaningful conclusions. As such, insufficient evidence exists 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; DRM = dosing regimen modification; VEGF = vascular endothelial growth factor.

Discussion Points

- The sponsor's request to reconsider the initial draft recommendation to reimburse aflibercept 8 mg with conditions for the treatment of DME was to revise the renewal and prescribing (dosing intervals) conditions. For the renewal, the sponsor requested that the condition requiring DME patients to achieve at least 15 letters gain at 6 months after starting aflibercept 8 mg to continue treatment with the drug be changed to the following: "aflibercept 8 mg should be renewed similarly to other anti-VEGFs currently reimbursed for the treatment of adult patients with DME." For dosing intervals, the sponsor requested that the condition for DME patients to be treated with aflibercept 8 mg no more frequently than every 12 weeks after the first 3 consecutive doses be modified to "injections should not be given more frequently than every 8 weeks." Details regarding the issues outlined in the sponsor's Request for Reconsideration have been provided below, after the Budget Impact in the Economic Evidence section.
- 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 noninferior (but not superior) to aflibercept 2 mg every 8 weeks in improving BCVA scores over baseline after 48 weeks treatment. The noninferiority benefit was maintained with high certainty at the week 60 assessment.
- At the initial meeting, CDEC recommended a threshold of a 15-letter improvement in BCVA at 6 months for renewal of reimbursement of aflibercept 8 mg in patients with DME based on information from a 2016 CADTH therapeutic review of anti-VEGF drugs for treating retinal conditions. At the

reconsideration, the committee agreed with the clinical expert that the threshold may not be achievable in some patients who otherwise qualify for treatment with aflibercept 8 mg. Therefore, CDEC considered it appropriate to remove the renewal condition and revise the discontinuation criteria based on the dosing regimen modification (DRM) strategy used in the PHOTON trial.

- 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 2 mg, noting that some newer anti-VEGF treatment for DME (e.g., faricimab) offer 12-week and 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 for patients and clinicians because it affects treatment burden and vision-related quality of life. The committee noted that a GRADE assessment found evidence supporting decreased injection frequency for aflibercept 8 mg compared to 2 mg in the PHOTON trial, which 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 clinical practice in Canada. 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.
- At the reconsideration meeting, CDEC discussed the sponsor's request to modify injection intervals every 12 weeks to no more frequently than every 8 weeks. The committee acknowledged the product monograph information stating that Eylea HD 8 mg (0.07 mL) may be administered every 8 to 16 weeks based on the physician's judgment of visual and anatomic outcomes. CDEC also recognized that some clinicians would like to prescribe aflibercept 8 mg every 8 weeks based on a treat-and-extend strategy. However, the committee discussed that most patients (91.0% in q12w and 89.1% in q16w arms) who completed treatment with aflibercept 8 mg in the pivotal PHOTON trial maintained their assigned treatment interval. The results from both arms were noninferior (and not superior) to aflibercept 2 mg, which was given at q8w. CDEC recognized that patients and providers have an unmet need for a drug with extended intervals between injections to reduce the treatment burden. However, several anti-VEGF drugs for the treatment of DME are already publicly reimbursed. The committee noted further that its initial decision to recommend reimbursing aflibercept 8 was primarily due to the drug's ability to meet this need, as demonstrated by achieving the noninferiority goal in the PHOTON trial when administered at every 12-week and 16-week intervals. Therefore, reducing the treatment interval to 8 weeks (i.e., the same dosing interval of aflibercept 2 mg) removes the advantage of aflibercept 8 mg and undermines a critical consideration for its reimbursement.
- CDEC discussed the importance of glycemic control to achieving optimal treatment outcomes and noted that the PHOTON trial excluded patients with hemoglobin A1C greater than 12%. However,

the committee agreed with the clinical expert consulted that glycemic control targets may vary for individual patients, making a single hemoglobin 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 should 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. Health Canada is currently reviewing biosimilars for aflibercept. 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

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 VEGF, further compromising the integrity of the blood-retina barrier. This condition is prevalent among adults in Canada, 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 noninvasive 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 a 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, as needed (PRN), and a treat-and-extend regimen where after initial treatment, the duration between doses is extended as much as possible while maintaining treatment response goals.

Aflibercept, 8 mg, is an anti-VEGF drug that received Health Canada notice of compliance 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 judgment of visual and anatomic outcomes. Treatment intervals of 1 month (4 weeks) for more than 3 consecutive doses have not been studied.

Aflibercept 2 mg 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 2 mg should be listed like 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 2 mg 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, noninferiority trial in adult patients (≥ 18 years) with DME involving the centre of the macula.
- One sponsor-submitted 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 Aging (IFA), and a commentary from the IFA).
- Input from public drug plans and cancer agencies participating in the CADTH review process.
- One clinical specialist with expertise in 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.
- Information submitted as part of the sponsor's Request for Reconsideration (described subsequently).
- Stakeholder feedback on the draft recommendation.

Stakeholder Perspectives

Patient Input

Input from the Canadian Council of the Blind, a joint patient input from FBC, the Canadian Council of the Blind, Vision Loss Rehabilitation Canada, Diabetes Canada, and the 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 postinjections. Some patients experienced notable visual complications such as scratchiness or pain in the eye following injections; others indicated that they could not complete at least 1 regular activity postinjection, such as watching television, reading, or driving and required assistance to carry out 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 with current therapies. 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 health care 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 a limited number of specialists. Therefore, any treatment that reduces physical, psychological, and logistical strain on patients and the health care 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 are 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 longer intervals between treatments to reduce treatment burden, with newer anti-VEGF drugs like faricimab and brolucizumab suggesting extended intervals of up to 12 or even 16 weeks. However, 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 8 mg to be used as a first-line treatment for DME or as an alternative when other treatments fail to provide control or pose too significant a patient burden. Aflibercept 8 mg 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, OCT measurements, and 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 the condition does not improve or worsen.

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, the Toronto Retina Institute, the Canadian Retina Society, the 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, an unmet need exists for efficacious and durable treatments that can reliably extend the treatment interval to minimize the 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-naive 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 anatomic outcomes. Eye anatomy will be measured via optical coherence tomography (OCTOBER) scans highlighted by 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 participating 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 8 mg:

- relevant comparators
- consideration for initiation of therapy
- consideration for discontinuation of therapy
- consideration for prescribing 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 III, multicentre, randomized, double-masked, active-controlled trial that assessed the	This is a comment from the drug plans to inform CDEC deliberations.

Drug program implementation questions	Clinical expert response
effectiveness, safety, and tolerability of a higher dose of aflibercept (8 mg) against the standard aflibercept (Eylea) 2 mg dose. It aimed to evaluate whether 2 extended dosing regimens of aflibercept 8 mg were at least as effective as Eylea 2 mg. No comparative trials were conducted between aflibercept 8 mg and other extended-interval anti-VEGF medications like brolucizumab-dbll and faricimab.	
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 µm—or 320 on Spectralis—confirmed by a reading centre at the screening visit. Additionally, patients must have a best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score ranging from 78 to 24, equivalent to a Snellen vision of 20/32 to 20/320, with vision loss attributed to DME.	This is a comment from the drug plans to inform CDEC deliberations.
The initiation criteria for treatments in the same category as aflibercept 8mg have changed. 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 a hemoglobin A1C level, a requirement that many jurisdictions have since removed. 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 applying aflibercept 8mg in treating 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 patients' eligibility to undergo laser photocoagulation. Current practices 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 essential in achieving optimal therapeutic outcomes. However, glycemic control can be achieved in a reasonable period. CDEC noted the importance of glycemic control; however, the committee agreed with the clinical expert that hemoglobin A1C levels should not be a patient-selection criterion for initiating aflibercept 8 mg treatment for DME.
Considerations for discontinuation of therapy	
Should discontinuation criteria be included in the recommendation?	The clinical expert noted that several key considerations should be considered when considering discontinuation. These would include decreasing visual acuity, the persistent or increased intraretinal or subretinal fluid, or the development of new subretinal hemorrhage despite active treatment. Typically, this assessment can take place after at least 3 injections. In such instances, it is important to consider either changing the therapy 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

Drug program implementation questions	Clinical expert response
	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 similarly 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 therapy	
The sponsor notes that aflibercept 8 mg meets an unmet need by having a dosing frequency 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 plans to inform CDEC deliberations.
Does aflibercept 8 mg meet an unmet need, given other products are marketed with an extended dosing interval?	The clinical expert noted that aflibercept 8 mg 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 noninferior, but not superior to aflibercept 2 mg. Also, evidence from the sponsor-submitted ITC was insufficient to suggest that either aflibercept 8 mg q12w or q16w is clinically superior or inferior to any other anti-VEGF treatments currently reimbursed for 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 q12w or q16w may not justify the additional cost, and there is a lack of evidence for the clinical benefit of every 16-week treatment against other anti-VEGFs.
System and economic issues	
Aflibercept 8 mg would have a 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 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 to avoid the recently implemented brolucizumab biosimilar switch initiative. It is expected that this would occur with aflibercept 8 mg. Question for CDEC: Should the pricing recommendation for reimbursement	Please refer to Table 1 for pricing conditions.

Drug program implementation questions	Clinical expert response
recommend that aflibercept 8 mg be negotiated to provide cost savings to drug programs relative to the cost of currently funded anti-VEGF drugs for DME.	
Confidential pricing agreements exist for most anti-VEGF drugs.	This is a comment from the drug plans to inform CDEC deliberations.
Retinal programs or provincial eye centres exist in a number of provinces. Bevacizumab's first policies were put 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 III, active-controlled, noninferiority, 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 q8w, aflibercept 8 mg q12w, or aflibercept 8 mg q16w, respectively. The primary outcome was a change from baseline in BCVA measured by the ETDRS letter score at week 48, and a key secondary outcome included a change from baseline in BCVA measured by the ETDRS letter score at week 60. Other secondary and exploratory outcomes relevant to this review included the proportion of participants with no intraretinal fluid (IRF) and no subretinal fluid (SRF) in the central subfield at week 48 and week 60, the 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 concerning baseline disease and demographic characteristics. Patients were numerically similar in age, with a slightly younger average in the aflibercept 8 mg q16w group (mean 61.9 years, SD 9.50) contrasted to the aflibercept 2 mg q8w (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 q12w [64.0%] and aflibercept 8 mg q16w [60.7%] groups contrasted to the aflibercept 2 mg q8w group [55.1%]). Most patients were white, with a numerically higher proportion in the aflibercept 8 mg q16w group (78.5%) compared to the aflibercept 2 mg q8w 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 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 PHOTON trial's primary noninferiority end point. The primary end point was met as treatment with aflibercept 8 mg q12w and q16w demonstrated noninferiority to aflibercept 2 mg q8w using a noninferiority 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 q12w and q16w arms, respectively, compared with 8.7 letters (SE = 0.73) in the aflibercept 2 mg q8w arm. Between-group differences in LS mean changes from baseline were −0.57 letters (95% CI, −2.26 to 1.13, noninferiority P value less than 0.0001) and −1.44 letters (95% CI, −3.27 to 0.39, noninferiority P value 0.0031) for the aflibercept 8 mg q12w and aflibercept 8 mg q16w arms, respectively, compared with the aflibercept 2 mg q8w arm. The supplementary per-protocol analysis was consistent with the main study.

Change from Baseline in BCVA at Week 60

The corresponding key secondary end point of change from baseline in BCVA at week 60 was met: treatment with aflibercept 8 mg q12w and aflibercept 8 mg q16w demonstrated noninferiority to aflibercept 2 mg q8w using a noninferiority 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 q8w arm. Between-group differences in LS mean changes from baseline were −0.88 letters (95% CI, −2.67 to 0.91, noninferiority P value 0.0003) and −1.76 letters (95% CI, −3.71 to 0.19, noninferiority P value 0.0122) letters for the aflibercept 8 mg q12w and aflibercept 8 mg q16w groups, respectively, compared to the aflibercept 2 mg q8w group.

Proportion of Patients Gaining at Least 15 ETDRS Letters at Week 60

At week 60, in the aflibercept 2 mg q8w group, 43 out of 165 patients (26.1%) gained at least 15 letters in BCVA from baseline. For the aflibercept 8 mg q12w group, 70 out of 326 patients (21.5%) showed at least a 15-letter gain. In the aflibercept 8 mg q16w group, 26 out of 163 patients (16.0%) recorded such gains. When comparing to the aflibercept 2 mg q8w 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 q12w group and −10.78% (95% CI, −19.27 to −2.29) for the q16w group. This was an exploratory end point.

Proportion of Patients With BCVA at Least 69 Letters at Week 60

At week 60, in the aflibercept 2 mg q8w group, 100 out of 165 patients (60.6%) had a BCVA of at least 69 ETDRS letters. For the aflibercept 8 mg q12w group, 211 out of 326 patients (64.7%) had a BCVA of at least 69 ETDRS letters. In the aflibercept 8 mg q16w group, 101 out of 163 patients (62.0%) recorded such scores. When comparing to the aflibercept 2 mg q8w group, the differences in proportions of patients with BCVA at least 69 letters at week 60 for the aflibercept groups were 4.34% (95% CI, −4.27 to 13.40) for the q12w group and 1.63% (95% CI,−8.91 to 12.17) for the q16w group. This was an exploratory end point.

Proportion of Patients Without Fluid at Foveal Centre at Week 60

Concerning the proportion of patients without fluid at the foveal centre (no IRF and no SRF) at week 60, 68.5% (113 out of 165) from the aflibercept 2 mg q8w group showed no fluid. In contrast, the aflibercept 8

mg q12w group had 61.8% (201 out of 325) without fluid, with a difference of −5.98% [redacted]. For the aflibercept 8 mg q16w 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 end point.

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 aflibercept 8 mg q12w and q16w 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 q12w and q16w arms respectively, compared with 9.8 (SD = [redacted]) in the aflibercept 2 mg q8w 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 q12w and q16w, respectively, compared to 3.05 (SE = [redacted]) in the aflibercept 2 mg q8w 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 q12w and aflibercept 8 mg q16w groups, respectively, compared to the aflibercept 2 mg q8w group.

Harms Results

Ocular TEAEs were reported in less than half of the enrolled patients. Specifically, 43.7% of patients (73 out of 167) in the aflibercept 2 mg q8w group experienced at least 1 ocular TEAE. This percentage was 44.8% (or 147 out of 328 patients) in the aflibercept 8 mg q12w group and the same percentage (44.8%, 73 out of 163 patients) in the aflibercept 8 mg q16w group. At least 1 ocular treatment-emergent SAE was reported in 0.6% of patients in the aflibercept 2 mg q8w group (1 out of 167 patients), 0.6% in the aflibercept 8 mg q12w group (2 out of 328 patients), and 1.2% in the aflibercept 8 mg q16w 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 q12w group), ulcerative keratitis (1 patient in aflibercept 2 mg q8w), and vitreous hemorrhage (1 patient in aflibercept 8 mg q16w).

19.2% of patients in the aflibercept 2 mg q8w group (32 out of 167 patients), 18.6% in the aflibercept 8 mg q12w group (61 out of 328 patients), and 16.6% in the aflibercept 8 mg q16w group (27 out of 163 patients) experienced nonocular SAEs.

Of adverse events of special interest, in the aflibercept 2 mg q8w group, 0.6% (1 out of 167 patients) of the participants experienced intraocular inflammation. In contrast, 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 q12w 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 q16w 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 endophthalmitis or retinal vasculitis cases were reported in any treatment group.

In the aflibercept 2 mg q8w 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 q12w 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 q16w 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 the PHOTON trial was appropriate for the study's objectives. Randomization was stratified by baseline 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 higher proportion of male patients and a higher proportion of white people in the higher dosage aflibercept groups contrasted to the aflibercept 2 mg q8w group. Statistical analytical approaches were similarly appropriate. Statistical analyses, including subgroup analyses, were predefined in the study protocol and the Statistical Analysis Plan. A hierarchical testing procedure was applied to primary and key secondary end points 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 complete analysis set and per-protocol set analyses indicated noninferiority of the aflibercept 8 mg given at 12 weeks or 16-week intervals. Missing data in primary and key secondary outcomes was addressed using Mixed-Model Repeated Measures 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. A hierarchical testing procedure accounted for adjustments for type I errors in the primary and key secondary end points. 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 end points.

The PHOTON trial included 4 sites in Canada. The inclusion and exclusion criteria, as well as the patient's baseline characteristics, were representative of Canadian patients. In addition, outcomes reported in the trial are clinically important outcomes and commonly utilized in clinical practice in Canada. Nonetheless, the trial dosing regimen of aflibercept 2 mg every 8 weeks does not correspond with the regimen practice in clinics in Canada, which follows a T and E 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 effectiveness and safety of aflibercept 8 mg versus other anti-VEGF therapies.

GRADE Summary of Findings and Certainty of the Evidence

The sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input from patient and clinician groups and public drug plans informed the selection of outcomes for GRADE assessment. 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 2 mg every 8 weeks in patients with DME.

Table 3: Summary of Findings for Aflibercept 8 mg Every 12 Weeks and Every 16 Weeks Versus Aflibercept 2 mg Every 8 Weeks for Patients With DME

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2 mg q8w	Aflibercept 8 mg q12w or q16w	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 8 mg q12w: 328 (1 RCT)	NA	8.7	8.1 (0.61)	0.57 fewer letters (2.26 fewer to 1.13 more)	High[a]	Aflibercept 8 mg q12w results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2 mg q8w.
	Aflibercept 8 mg q16w: 163 (1 RCT)	NA	8.7	7.2 (0.71)	1.44 fewer letters (3.27 fewer to 0.39 more)	High[a]	Aflibercept 8 mg q16w results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2 mg q8w.
Change from baseline in BCVA, LS mean (SE) letters Follow-up: 60 weeks (0 [worst] to 100 [best])	Aflibercept 8 mg q12w: 328 (1 RCT)	NA	9.4	8.5 (0.63)	0.88 fewer letters (2.67 fewer to 0.91 more)	High[a]	Aflibercept 8 mg q12w results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2 mg q8w.
	Aflibercept 8 mg q16w: 163 (1 RCT)	NA	9.4	7.6 (0.75)	1.76 fewer letters (3.71 fewer to 0.19 more)	High[a]	Aflibercept 8 mg q16w results in little-to-no clinically important difference in the change in BCVA when compared with aflibercept 2 mg q8w.

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2 mg q8w	Aflibercept 8 mg q12w or q16w	Difference		
Proportion of patients without fluid at the foveal centre*							
Proportion of patients without fluid at the foveal centre Follow-up: 60 weeks	Aflibercept 8mg q12w: 328 (1 RCT)	0.90 [redacted]	68.5 per 100	61.8 per 100 (NR)	5.98 fewer per 100 [redacted]	Moderate[b]	Aflibercept 8 mg q12w likely decreases the proportion of patients without fluid at the foveal centre compared with aflibercept 2 mg q8w. The clinical importance of this decrease is uncertain.
	Aflibercept 8 mg q16w: 163 (1 RCT)	0.85 [redacted]	68.5 per 100	58.0 per 100 (NR)	9.88 fewer per 100 [redacted]	Moderate[b]	Aflibercept 8 mg q16w likely decreases the proportion of patients without fluid at the foveal centre compared with aflibercept 2 mg q8w. The clinical importance of this decrease is uncertain.
Proportion of patients with ETDRS letters gain*							
Proportion of patients gaining ≥ 15 letters in BCVA from baseline Follow-up: 60 weeks	Aflibercept 8 mg q12w: 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 8 mg q12w will likely decrease the proportion of patients gaining ≥ 15 letters from baseline compared with aflibercept 2 mg q8w. The clinical importance of this decline is uncertain.
	Aflibercept 8 mg q16w: 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 8 mg q16w results in a decrease in the proportion of patients gaining ≥ 15 letters from baseline when compared with aflibercept 2 mg q8w. The clinical importance of the decrease is uncertain.

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2 mg q8w	Aflibercept 8 mg q12w or q16w	Difference		
Proportion of patients with BCVA ≥ 69 letters Follow-up: 60 weeks	Aflibercept 8mg q12w: 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 8 mg q12w likely increases the proportion of patients with ≥ 69 letters when compared with aflibercept 2 mg q8w. The clinical importance of the increase is uncertain.
	Aflibercept 8mg q16w: 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 q16w may result in an increase in the proportion of patients with ≥ 69 letters when compared with aflibercept 2 mg q8w.
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 8 mg q12w: 328 (1 RCT)	NA	3.05	4.55 [redacted]	1.50 more points ([redacted]	High[e]	Aflibercept 8 mg q12w results in little-to-no clinically important difference in the change from baseline in vision-related QoL when compared with aflibercept 2 mg q8w.
	Aflibercept 8 mg q16w: 163 (1 RCT)	NA	3.05	3.21 [redacted]	0.17 more points [redacted]	High[e]	Aflibercept 8 mg q16w results in little-to-no clinically important difference in the change from baseline in vision-related QoL when compared with aflibercept 2 mg q8w.
Number of active injections*							
Number of active injections, LS mean	Aflibercept 8 mg q12w: 289 (1 RCT)	NA	9.8	7.0 ([redacted])	2.8 fewer injections ([redacted]	Low [f]	Aflibercept 8 mg q12w likely decreases the frequency of injections when compared with

Outcome and follow-up	Intervention: Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Aflibercept 2 mg q8w	Aflibercept 8 mg q12w or q16w	Difference		
(95% CI) Follow-up: 60 weeks					[redacted])		aflibercept 2 mg q8w. The clinical importance of the decrease is uncertain.
	Aflibercept 8 mg q16w: 152 (1 RCT)	NA	9.8	6.0 ([redacted])	3.8 fewer injections ([redacted])	Low[f]	Aflibercept 8 mg q16w likely decreases the frequency of injections when compared with aflibercept 2 mg q8w. The clinical importance of the decrease is uncertain.
Ocular serious adverse events							
Proportion of patients with ocular SAEs Follow-up: 60 weeks	Aflibercept 8mg q12w: 328 (1 RCT)	NR	0.6 per 100	0.6 per 100 (NR)	NR	Low[g]	Aflibercept 8 mg q12w may be used by a similar proportion of patients with ocular SAEs as compared with aflibercept 2 mg q8.
	Aflibercept 8 mg q16w: 163 (1 RCT)	NR	0.6 per 100	0.6 per 100 (NR)	NR	Low[g]	Aflibercept 8 mg q16w may be associated with a similar proportion of patients with ocular SAEs to aflibercept 2 mg q8w.

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; q8w = every 8 weeks; q12w = every 12 weeks; q16w = every 16 weeks; 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 4 letters (i.e., the noninferiority margin); the point estimate and entire CI suggest little-to-no difference.

[b]No published between-group minimal important difference (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 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. It was not rated down for imprecision; a between-group difference of less than the null and a CI that excludes the null suggest harm compared to aflibercept 2 mg q8w.

[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 levels for very serious imprecision as the CI is very wide and contains the potential for considerable harm in the lower bound of the CI. In contrast, 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 CI suggest little-to-no difference.

[f]Rated down 1 level for serious concerns about the 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. It 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 a minimal number of events.

*Not part of predefined statistical testing in the trial.

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

Long-Term Extension Studies

The sponsor submitted no long-term extension studies.

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 every 12 weeks and every16-week treatment 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. Different statistical models and links were applied depending on the outcome type, including average 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: 1 assessed aflibercept 8 mg, 11 assessed aflibercept 2 mg, 6 assessed ranibizumab, 2 assessed faricimab, 9 assessed laser PRN, 2 assessed brolucizumab, and 2 assessed bevacizumab. Risk of bias assessment of the included studies in the sponsor ITC determined that 2 studies were of high risk as defined 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 a 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 favourable results in letters gained for aflibercept 2 mg every 4 weeks compared to aflibercept 8 mg and favourable results for aflibercept 8 mg when compared to laser in the outcome of BCVA. In the outcome of letters gained, aflibercept 8 mg q12w showed an unfavourable response against aflibercept 2 mg q4w [redacted] and a favourable response against laser [redacted] Aflibercept 8 mg q16w showed an unfavourable response against aflibercept 2 mg q8w [redacted] and against aflibercept 2 mg q4w [redacted] and shows a favourable OR versus laser [redacted]

Based on predetermined injection 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 as-needed regimens are not predetermined and show a mean number of injections between 7.41 and 9.18 across the first year and a mean number of

injections between 3.79 and 5.80 across the interventions in the second year. Absolute noncomparative results of injection frequency suggest that aflibercept 8 mg q12w has a mean injection frequency of 6.00 in the first year and 3.50 in the second year, while every 16-week treatment 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 credible intervals, except for the ocular severe adverse event comparison against bevacizumab, which shows favourable results to aflibercept 8 mg. The 95% CrIs were wide for other comparisons, suggesting either treatment could be favoured. No other safety end point was reported.

Critical Appraisal

The systematic literature review supporting the sponsor-submitted 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 reduce the applicability of the findings to clinical settings in Canada, favouring 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 heterogeneous 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.), The absence of comparative data for injection frequency limits the interpretability of aflibercept 8 mg's potential benefits in reducing injection frequency versus other interventions and regimens.

Studies Addressing Gaps in the Evidence from the Systematic Review

The sponsor submitted no studies addressing gaps in the systematic review evidence.

Economic Evidence

Table 4: 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 • A sponsor-submitted ITC informed comparative clinical efficacy (change in BCVA) and administration frequency
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 of 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
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; q12w = every 12 weeks; q16w = 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 the 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. Without more reliable input values to estimate the key parameters of the budget impact analysis, 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 introducing 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 the 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 3 years of reimbursement. As such, whether there are cost savings and the extent of any savings realized by the drug plans is highly uncertain.

Request for Reconsideration

The sponsor filed a Request for Reconsideration of the draft recommendation for aflibercept 8 mg for the treatment of DME. The sponsor requested that CDEC reconsider their review of aflibercept 8 mg and the conditions for reimbursement based on the following:

- The sponsor believes that achieving at least 15-letters gain in BCVA by month 6 is not based on current evidence to determine adequate response for continuation (i.e., renewal) of anti-VEGF treatment. The sponsor believes that a 5 to 10-letter gain can provide additional patient benefits.
- The sponsor believes that a prescribing condition stating that injections should not be given more frequently than 12-week intervals does not align with the dosage recommendation in the Health Canada product monograph or how patients are treated in clinical practice using a treat-and-extend approach.

In the meeting to discuss the sponsor's Request for Reconsideration, CDEC considered the following information:

- Information from the initial submission related to the issues identified by the sponsor.
- Feedback on the draft recommendation from the sponsor.
- Feedback on the drug recommendation from the public drug plans.
- Feedback from 1 clinical expert with expertise in diagnosing and treating patients with DME.
- Feedback on the draft recommendation from 19 clinician groups as part of the feedback on the draft recommendation. Feedback was received from the following clinician groups: Apex Eye Institute; Southwestern Ontario Community Ophthalmologists; Retina Division of the Ottawa Hospital;

Toronto Ophthalmologists; Toronto Retina Institute; Scarborough Ophthalmologists; Canadian Ophthalmological Society; Canadian Retina Society; Niagara Ophthalmologists; Saskatchewan Health Authority; EPSNB; Dr. Kathy Cao; Retina Specialists – Dalhousie; Retina Specialists of Vancouver Island Health Authority; Atlantic coast retina consultants; Central Alberta Eye Surgery and Clearfield Eye Physicians and Surgeons; Northeastern Ontario Ophthalmology group; Waterloo Eye; and West Coast Retina Consultants Inc.

- One joint feedback on the draft recommendation from 5 patient groups: FBC, the Canadian Council of the Blind, CNIB, Vision Loss Rehabilitation Canada, International Federation of Aging.

All stakeholder feedback received in response to the draft recommendation is available on the CADTH website.

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.

Initial meeting date: January 25, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

Reconsideration meeting date: May 23, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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