Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

aflibercept 8mg/0.07mL (Eylea HD)

Bayer Inc.

Indication: Treatment of diabetic macular edema (DME).

September 1, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Aflibercept 8mg
Indication: Age-related Macular Degeneration (AMD) and Diabetic Macular Edema (DME)
Name of Patient Group: The Canadian Council of the Blind
Author of Submission: Keith D. Gordon Ph.D., Senior Research Officer, Canadian Council of the Blind.

1. About Your Patient Group

The Canadian Council of the Blind (CCB) was founded in 1944 by schools of the blind and by returning blind Canadian war veterans and is recognized as the Voice of the Blind™ in Canada. The CCB is a membership-based not-for-profit, that brings together Canadians who are living with vision loss, those who are blind, deaf-blind, and the partially sighted. In doing so the Council maintains a vibrant network of active members in 80 chapters across Canada. Each chapter is unique to its geographic area and engages in a variety of social, recreational and community activities based on the interests of their local members.

A tireless advocate of the vision loss community the CCB works to promote a sense of purpose and self-esteem along with enabling the efforts of each member to achieve an enhanced quality of life. The Council through its lived experience constituency is proud of its efforts to break down barriers and remains dedicated to building public awareness and improving the well-being of people with seeing disabilities.

The Canadian Council of the Blind offers numerous programs to assist people living with vision loss, increase accessibility in all areas of vision loss life and bring awareness of vision issues to the public and government. The CCB leads initiatives that call for the provision of the very best in available medical treatments, research, and the fostering of patients' rights without limitation or discrimination. It does this all while recognizing that vision loss and blindness are preventable.

2. Information Gathering

The surveys conducted with patients with AMD and DME were reported in a joint survey submitted to CADTH in a separate submission by Fighting Blindness Canada. Data from these surveys were obtained during the first months of 2020.

CCB Surveys discussed below were obtained as follows:

a. The impact of the COVID-19 pandemic on Canadians who are blind, deaf-blind and partially sighted. April 2020. Number of respondents to survey: 572. Available at: https://ccbnational.net/shaggy/wp-content/uploads/2023/07/3-COVID-19-Survey-Report-Final-wb.pdf)

b. A report card on vision health in Canada. Part 2. The impact of the COVID-19 pandemic on Canadians who are blind, deaf-blind or partially sighted 2022. June, July 2022. Number of respondents to survey: 572 (exactly the same number as the 2020 survey). Available at: https://ccbnational.net/shaggy/wp-content/uploads/2023/07/16-Report-Card-on-Vision-Health-in-Canada-2021-Part-2-English-Oct-14-20222.pdf.

c. A report card on vision health in Canada. Part 1. The impact of the COVID-19 pandemic on vision health in Canada 2021. Report published October 2022. Available at: https://ccbnational.net/shaggy/wp-content/uploads/2023/07/15-Report-Card-on-Vision-Health-in-Canada-2021-Part-1-English-Oct-14-2022.pdf

3. Disease Experience

In a separate submission, in collaboration with Fighting Blindness Canada, we reported on a survey conducted with patients with AMD, as well as a separate survey conducted with patients with Diabetic Retinopathy and/or Diabetic Macular Edema. It is not intended to repeat the findings of these surveys in the current submission. However, some of the key findings of these surveys will be included in the discussion below.

These surveys were conducted prior to the onset of the COVID-19 pandemic. Since that time CCB has conducted two surveys of people living with vision loss to ascertain the impact that the pandemic was having on their lives. The first survey, conducted in April 2020, revealed that the vision loss community was significantly stressed. Among the fairly long list of concerns expressed by respondents to the survey was the concern that people had about going out of their homes for any activity, as, under social distancing recommendations, they were not allowed to have an accompanying person. They were also worried about having someone accompany them if they had to go to a doctor or a hospital, and they were worried about getting transportation if they had to go to a doctor or a hospital. Concern was expressed by some respondents that they might lose vision due to their not getting their regular injections. This survey reported a general feeling of loneliness and isolation among people living with vision loss.

In order to assess whether the situation had changed as the pandemic progressed, an almost identical survey was conducted in June and July 2022. This survey revealed that there was an improvement in stress levels in this patient group, however there was still a significant number of people living with loneliness and feelings of isolation.

The main healthcare issue concerning most respondents to the 2022 survey was that they may not be able to see their doctor if they became sick during the pandemic. Many respondents were concerned about being able to access transportation to get to a doctor or hospital. They were also concerned about having someone accompanying them to the doctor or hospital and respondents said that they had had an important medical appointment or surgery cancelled due to the pandemic.

An analysis of the impact of the pandemic on the state of vision health in Canada at the end of 2021 revealed that a significant backlog in eye surgeries and visits to eye doctors still existed in 2021. Many ophthalmologists interviewed for this study reporting that they had patients who had experienced significant vision loss as a result of missed visits for injections.

4. Experiences With Currently Available Treatments

While the CCB has no experience with currently available treatments, the clinical studies for aflibercept 8mg show it to be equivalent in safety and efficacy to the currently available aflibercept 2mg, even when used less frequently.

In the surveys discussed in section 3 above, it was found that patients with AMD experienced significant disruption to conducting their normal daily activities due to their sight loss. The sight loss caused them to live with continual worry about possible further sight loss; they needed to rely on others to conduct many of their activities and as a result felt very lonely and isolated.

These surveys revealed that a significant number of patients were missing their regular eye injections, the most common reason given being their inability to get someone to accompany them to get their injection. These studies were conducted prior to the pandemic. The CCB study discussed above showed that people were experiencing much greater difficulty getting someone to accompany them during the pandemic. All this points to the benefit provided by a treatment that will minimize the number and frequency of injections required.

The backlog in ophthalmologists' offices and surgeries reported in the CCB Report Card further argues for the benefit provided by a treatment that will reduce the number of people "battling the backlog" in order to receive their essential anti-VEGF injections.

5. Improved Outcomes

As reported above, people who experience sight loss due to AMD or DME are significantly affected in their ability to conduct their daily activities. The inability to access transportation to get to their doctor results in many people missing essential appointments. This was exacerbated during the pandemic. The CCB patient survey revealed that many people were still concerned about going out of their houses and attending ophthalmologists' visits. A reduction in the number of visits a patient requires will undoubtedly lead to fewer missed appointments and improved outcomes.

Discussions with ophthalmologists over the past few years reveal that many ophthalmologists have had patients who did not respond to one anti-VEGF treatment subsequently respond to another treatment when switched. The availability of one more anti-VEGF treatment will increase the number of possible switches and is sure to offer more effective outcomes for a small number of patients.

6. Experience With Drug Under Review

The patients surveyed in the studies discussed above had no experience with aflibercept 8mg.

7. Companion Diagnostic Test

Not applicable

8. Anything Else?

As discussed above, the CCB Report Card showed a large backlog in the number of eye surgeries, coupled with an inability to overcome this backlog. The availability of a new medication that will decrease the number of patients being seen by retinal specialists for anti-VEGF injections should free up ophthalmologists' time for surgery and other backlogged treatments, thereby improving vision health for all patients.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novartis				X

Bayer				X
AbbVie				X
Roche				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Keith Gordon
Position: Senior Research Officer
Patient Group: Canadian Council of the Blind
Date: 4 August 2023

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: aflibercept (8mg)
Indication: diabetic macular edema
Name of Patient Group: Fighting Blindness Canada, The Canadian Council of the Blind, CNIB, Vision Loss Rehabilitation Canada, Diabetes Canada, International Federation on Ageing
Author of Submission: Dr. Larissa Moniz (FBC), Jim Prowse (CCB), Thomas Simpson (CNIB), Jennifer Urosevic (VLRC), Laura Hoffe (DC), Jane Barratt (IFA)

1. About Your Patient Group

Fighting Blindness Canada (FBC) is the largest charitable funder of vision research in Canada.

Over our 49-year history, FBC has contributed critical funding for the development of sight-saving treatments and cures for blinding eye diseases. By raising and stewarding funds, FBC is helping drive forward research that supports our goal of understanding why vision loss occurs, how it can be slowed and how sight can be restored.

We are an invaluable resource for individuals and families impacted by blindness, providing accurate eye health information through our website and educational events, as well as engaging with government and other stakeholders to advance better vision health policies.

The Canadian Council of the Blind (CCB) was founded in 1944 by schools of the blind and by returning blind Canadian war veterans and is recognized as the Voice of the Blind™ in Canada. The CCB is a membership-based not-for-profit, that brings together Canadians who are living with vision loss, those who are blind, deaf-blind, and the partially sighted. In doing so the Council maintains a vibrant network of active members in 80 chapters across Canada. Each chapter is unique to its geographic area and engages in a variety of social, recreational and community activities based on the interests of their local members.

A tireless advocate of the vision loss community the CCB works to promote a sense of purpose and self-esteem along with enabling the efforts of each member to achieve an enhanced quality of life. The Council through its lived experience constituency is proud of its efforts to break down barriers and remains dedicated to building public awareness and improving the well-being of people with seeing disabilities.

The Canadian Council of the Blind offers numerous programs to assist people living with vision loss, increase accessibility in all areas of vision loss life and bring awareness of vision issues to the public and government. The CCB leads initiatives that call for the provision of the very best in available medical treatments, research, and the fostering of patients' rights without limitation or discrimination. It does this all while recognizing that vision loss and blindness are preventable.

Founded in 1918, **CNIB** is a non-profit organization driven to change what it is to be blind today. We deliver innovative programs and powerful advocacy that empower people impacted by blindness to live their dreams and tear down barriers to inclusion. Our work as a blind foundation is powered by a network of volunteers, donors and partners from coast to coast to coast.

Vision Loss Rehabilitation Canada (VLRC) is a health services organization. We provide training that enables people who are blind or partially sighted to develop or restore key daily living skills, helping enhance their independence, safety and mobility. Our certified specialists work closely with ophthalmologists, optometrists and other health care professionals, providing essential care on a referral basis in homes and communities.

The Vision of VLRC is to maximize health and independence for Canadians impacted by vision loss and our mission is to provide high-quality, integrated and accessible rehabilitation and health care services that enable Canadians impacted by vision loss to live the lives they choose.

Diabetes Canada (DC) is a national health charity representing millions of Canadians affected by diabetes. Diabetes Canada leads the fight against diabetes by helping people live healthy lives, preventing the onset and consequences of diabetes, and discovering a cure. It has a heritage of excellence and leadership, and its co-founder, Dr. Charles Best, along with Dr. Frederick Banting, is credited with the co-discovery of insulin. Diabetes Canada is supported in its efforts by a community-based network of volunteers, employees, health care professionals, researchers, and partners. By providing education and services, advocating on behalf of people living with diabetes, supporting research and translating it into practical applications, Diabetes Canada is delivering on its mission. Diabetes Canada will continue to change the world for those affected by diabetes through healthier communities, exceptional care, and high-impact research.

The **International Federation on Ageing** **(IFA)** is an international non-governmental organization (NGO) based in Canada whose members are government, NGOs, academia, industry, and individuals in nearly 80 countries. IFA believes that all these members working together are essential to help shape and influence policy and good practices. IFA stands to drive the agenda for the world's population ageing. We are proud to have general consultative status at the United Nations. The International Federation on Ageing is a non-State actor in official relations with the World Health Organization (WHO).

Vision health is one of IFAs priorities. Since its inception in 2016, the Eye See You: Advocating for Options in Eye Health campaign has become known for collaborating across sectors and disciplines on matters that impact the vision health of all Canadians, but in particular retinal diseases often affecting older age groups and those with diabetes. IFAs four-pronged approach to this growing issue remains current today in building community and influencing vision health policy and practice: 1. Supporting patients (and their families) to make informed choices regarding their vision health; 2. Raising awareness on the availability of safe and effective vision treatments; 3. Leading advocacy efforts on issues affecting vision health in an ageing population; and 4. Enriching the discourse on vision health by building connections across disciplines and sectors

2. Information Gathering

Data shared in this submission were collected through an online survey made available to Canadians living with diabetic retinopathy (DR) or diabetic macular edema (DME) during the first months of 2020. Shared across networks

associated with the submitting organizations, the survey is part of a larger research project titled VIEW DR/DME (Valuation and Interpretation of Experiences with DR/DME) that received ethics approval from Advarra, one of the largest independent providers of institutional review board (IRB) services in Canada.

The intent of the survey was to learn more about the lived experiences of Canadians living with DR and DME. While the goal was not to learn more about experiences of any specific treatment we did gather data and insights related to experiences of injections in general. We asked respondents to indicate which anti-VEGF they may have received. Since this survey was completed in early 2020, it is assumed that those that indicated using aflibercept (Eylea), received aflibercept (2mg) and not the drug under review aflibercept (8mg).

Instead, the data and analysis that follows provide insights into the lives of those who live with DR and DME, and who must manage and navigate the often-daily barriers and burdens that accompany these diseases. Our belief is that these perspectives are crucial, and that they can be used to guide decision-making related to treatments that can address the physical, psychological, and socioeconomic burdens associated with DR and DME.

Overview of Respondents

A total of 67 Canadians responded to the survey. As DR affects approximately 500,000 Canadians,[1] this number may seem small, but it is difficult locating and engaging with individuals with DR and DME, at least partially as a result of low disease awareness. These challenges have been discussed in various research efforts, including an article published recently by researchers associated with FBC.[2]

Out of these respondents, most were between either 61-80 (44.4%) or 41-60 years of age (37%), with a mean age of 56.8 (SD = 13.2). Most were either working full time (38.9%) or retired (33.3%), and a majority resided in urban regions within Ontario (41.8%), British Columbia (14.9%), Alberta (13.4%), and Quebec (11.9%), followed by smaller groups within other provinces.

Table 1. Baseline characteristics of respondents (n = 67)

Characteristic	n (%)
Age (n = 54)	
Mean age (SD)	56.8 (13.2)
18 - 40 years	9 (16.7)
41 - 60 years	20 (37.0)
61 - 80 years	24 (44.4)
Over 80 years	1 (1.9)
Biological Sex (n = 54)	
Female	23 (42.6)
Male	31 (57.4)
Intersex	0 (0.0)

[1] Ballios BG, Park T, Chaudhary V, Hurley B, et al. Identifying gaps in patient access to diabetic screening eye examinations in Ontario: a provincially representative cross-sectional study. *Can J Ophthalmol*. 2021;56(4):223-230. https://doi.org/10.1016/j.jcjo.2020.10.018

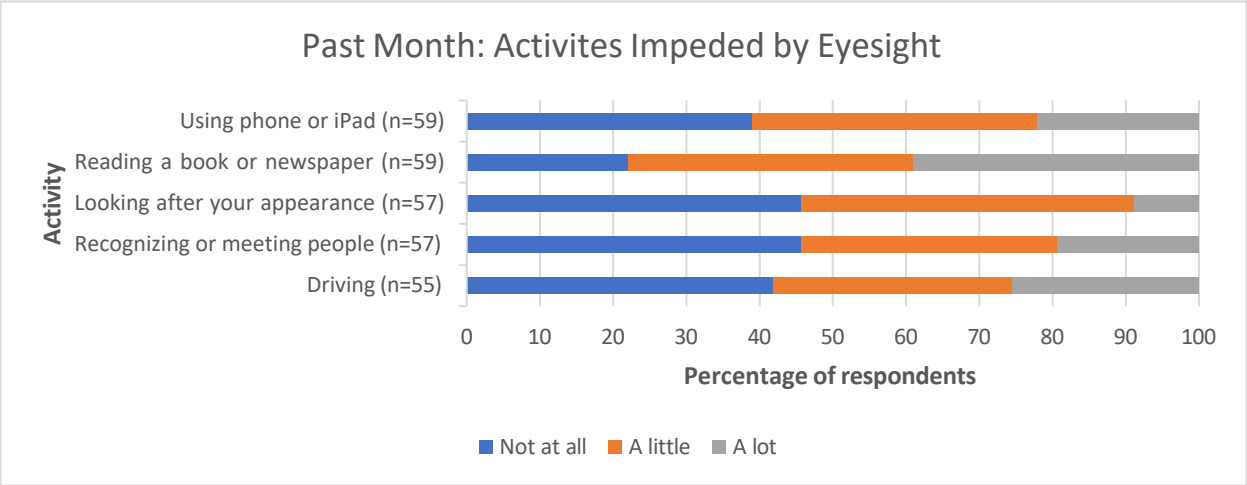
[2] Andrews C, Yoganathan P, Pereira JA. Blind Spots: Gaps in Disease Knowledge and the Role of Patient Education for Canadians with Diabetic Macular Edema. *Can J Diabetes*. 2021;45(4):375-378. doi: 10.1016/j.jcjd.2020.10.001

Province (n = 67)	
Ontario	28 (41.8)
British Columbia	10 (14.9)
Alberta	9 (13.4)
Quebec	8 (11.9)
Manitoba	3 (4.5)
Nova Scotia	3 (4.5)
Newfoundland	2 (3.0)
Yukon	2 (3.0)
New Brunswick	1 (1.5)
Saskatchewan	1 (1.5)
Location (n = 67)	
Urban	62 (92.5)
Rural	5 (7.5)
DME/DR in one eye or both eyes (n = 67)	
Both eyes	51 (76.1)
One eye	10 (14.9)
I don't know	6 (9.0)
Other household members (n = 60)	
Partner/spouse	43 (71.7)
My child(ren)	16 (26.7)
No one	9 (15.0)
Family member(s) other than partner and child	3 (5.0)
I live in a retirement home	2 (3.3)
Roommate/friend	2 (3.3)
I live in a nursing home/long-term care facility	1 (1.7)
Employment Status (n = 54)	
Retired	18 (33.3)
Employed, working full-time	21 (38.9)
Employed, working part-time	0 (0.0)
Not employed, looking for work	2 (3.7)
Student	1 (1.9)
Unemployed due to illness or disability	8 (14.8)
Homemaker	0 (0.0)
Parental leave	0 (0.0)
Taking care of a family member	1 (1.9)
Other: *Employed but on disability (2), self-employed (1)*	3 (5.6)

3. Disease Experience

Respondents made it clear that both DR and DME have substantial and life-altering impacts on daily life. When asked which activities are most impacted by their condition, they emphasized effects on reading, using a phone, and driving, activities that many individuals take for granted.

Figure 1. Activities Impeded by Eyesight



These difficulties were also framed in terms of "challenges." When asked about the kinds of challenges they face as a result of DR or DME, over 80% (8 out of 10) selected "worry that my condition might worsen in the future", followed by "not being able to do the daily activities I used to" (45.9%) and "explaining my condition to family and friends" (36.1%).

Table 2. Challenges with DMR/DR (n = 61)

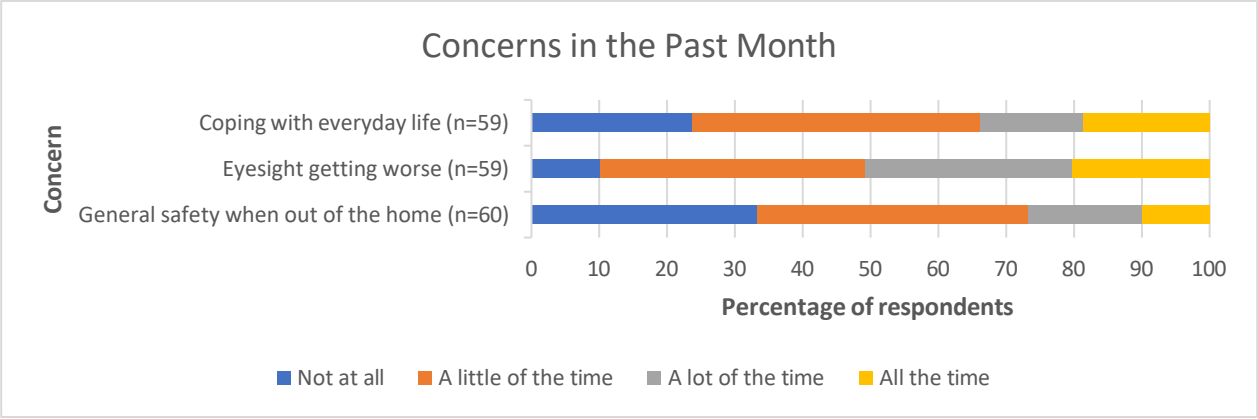
Challenges	n (%)
Worry that my condition might worsen in the future	49 (80.3)
Not being able to do the daily activities I used to	28 (45.9)
The long wait times for appointments	18 (29.5)
Explaining my condition to family and friends	22 (36.1)
Lack of social support	14 (23.0)
Finding answers to my questions about my condition	18 (29.5)
Socializing	19 (31.1)
Other*	5 (8.2)

**Getting the test I need prior to injections, working/finding work, no funding for technology or training, how long it takes to learn technology, getting appointments with my very busy retinologist*

Worrying about whether the condition will worsen implies the existence of emotional and psychological burdens as well. DR and DME may affect daily life as a result of lower visual acuity, but they may also lead to significant psychological strain in the form of a generalized anxiety related to the future. Furthermore many respondents are concerned about their eyesight worsening "all the time" or "a lot of the time" and emphasized the real challenges of "coping with everyday life" and "general safety when out of the home."

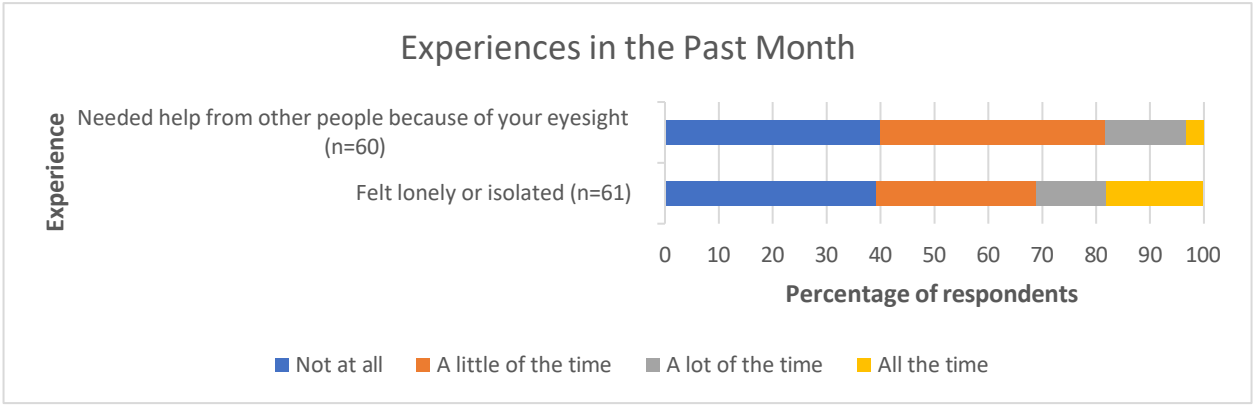
Recognizing that both DR and DME are complications of diabetes, it is useful to frame these considerations within the broader experiences of diabetes as a complex and impactful disease. Common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination and weight change (gain or loss). Diabetes requires considerable self-management, including eating well, engaging in regular physical activity, maintaining a healthy body weight, taking medication as prescribed, monitoring blood glucose, and managing stress. When Diabetes Canada asked Canadian diabetes patients how the disease impacts their lives, several described diabetes as a condition that must be dealt with 24 hours a day, 7 days a week, 365 days a year with no breaks and no holidays or time off. It is physically and mentally exhausting.

Figure 2. Concerns in the Past Month



It is clear that DR and DME weigh heavily on the minds of affected individuals, here shown as persistent emotional and psychological factors which is exemplified by feelings of loneliness and isolation. In the survey most respondents reported needing assistance and feelings of isolation at least “a little of the time.”

Figure 3. Experiences of Dependence and Isolation



The experience of needing help also highlights the social dimensions of DR and DME, implying that the impacts of the diseases extend beyond one’s personal life to touch on friends and family members. Any analysis of these diseases

should take into account the social dimensions of lived experience that are common across eye disease that affect visual acuity and make daily life more challenging.

Overall, it is clear that DR and DME have significant and life-altering impacts on the lives of those who are affected by them. Whether it be in relation to reading or worrying or relying on others, the diseases tend to affect the details and complexities of everyday living in a pervasive manner (as opposed to being a secondary or background consideration). For this reason, it is reasonable to conceptualize DR and DME as considerable burdens on the daily lives of patients.

4. Experiences With Currently Available Treatments

Over one-half of survey participants (56.4%) indicated that they currently receive injections as a treatment for DR or DME, with the most common brand being Lucentis (29.4%), followed by aflibercept (Eylea) (24.6%), Avastin (20.2%), and Ozurdex (13.5%). The remainder of patients indicated that they did not know the brand of their injection. As noted above, due to the timeline of the study, it is assumed that participants who indicated receiving aflibercept, received aflibercept (2mg) and not the drug under review (aflibercept (8mg)).

Most respondents selected that their last injection was 1-5 years ago (26.9%), followed by more than 5 years ago (16.4%), 3-11 months ago (10.4%), and less than 3 months ago (4.5%).

Table 3. Timing of first injection (n = 67)

First Injection	n (%)
Less than 3 months ago	3 (4.5)
3-11 months ago	7 (10.4)
1-5 years ago	18 (26.9)
More than 5 years ago	11 (16.4)
I've never received injections for DME or DR	28 (41.8)

The low number of respondents (4.5%) who received injections more recently is disconcerting, potentially indicating high drop-off and nonadherence in relation to injections. If this is the case, it aligns with existing research showing that nonadherence to intravitreal injections is quite high.[3]

Satisfaction, Adherence, and Assistance

The largest number of respondents showed that they are "satisfied" with their injections (54.5%) and that "they helped me avoid losing more eyesight" (63.6%).

Table 4. Level of satisfaction with injections (n = 22)

	n (%)
Very dissatisfied	1 (4.5)
Dissatisfied	1 (4.5)

[3] Okada M, Mitchell P, Finger RP, Eldem B, et al. Nonadherence and Nonpersistence to Intravitreal Injection Therapy for Neovascular Age-Related Macular Degeneration: A Mixed-Methods Systematic Review. *Ophthalmology*. 2021;128;2;234-247. https://doi.org/10.1016/j.ophtha.2020.07.060

Neither satisfied nor dissatisfied	7 (31.8)
Satisfied	12 (54.5)
Very satisfied	1 (4.5)

Table 5. How the injections have helped (n = 22)

	n (%)
They helped me avoid losing more eyesight	14 (63.6)
They dried up fluid/blood in my eye(s)	10 (45.4)
They improved my eyesight	7 (31.8)
They have had no effect but I receive injections because my doctor recommends them	3 (13.6)
I don't know	1 (4.5)
Other*	3 (13.6)

**Think it's helping, stopped proliferation of blood vessels, have tunnel vision in one eye but it started to get tightened much more than last year*

A majority of respondents who receive injections also indicated that they have not missed an injection in the last year (68.2%). Despite this, the number of patients who have missed injections is sizeable (31.8%) and deserving of attention. Further, in a similar study on AMD conducted by our groups, the percentage of missed appointments was just below 20%. It is worth considering why patients with DR and DME appear to be missing more appointments than those with AMD. Clearly, missed injection appointments—and by extension all forms of nonadherence and non-persistence—require serious attention when developing policies and treatments for DR and DME and support the development and approval of new treatments which can reduce treatment burden.

Following up on this, our survey asked respondents why they have cancelled or delayed appointments in the past. Although the response rate for this question was quite low, most respondents indicated that they were too busy to attend the appointment (50%), not feeling well (33.3%), being "unable to find someone to take me to the appointment" (16.7%), and being "scared to receive the injection" (16.7%).

Table 6. Reason for cancellation or delay (n = 6)

Reason	n (%)
Unable to find someone to take me to the appointment	1 (16.7)
Unable to travel to appointment	0 (0.0)
Could not afford attending the appointment	0 (0.0)
Too busy to attend appointment	3 (50.0)
Did not know how important the injection was to my sight	0 (0.0)
Scared to receive the injection	1 (16.7)
Did not find previous injections helpful	0 (0.0)
I forgot about the appointment	0 (0.0)
I was not feeling well	2 (33.3)
Other	0 (0.0)

Regarding the inability to find someone to assist with travel, our questions did uncover a significant reliance on assistance in this area. When asked who helps them attend their injections appointments, over 80% indicating

receiving travel assistance from either a spouse, family member, or friend. These individuals helped in a number of ways, including with travel (93.3%), with waiting at the appointment (80%), and with assistance in everyday tasks after the injection (33.3%).

Table 7. Type of help provided (n = 15)

	n (%)
Help me after the injections with everyday tasks	5 (33.3)
Wait with me at the appointment	12 (80.0)
Travel with me or drive me to/from the appointment	14 (93.3)
Take care of things at home while I am away	1 (6.7)
Physical support at my appointment	4 (26.7)
Other	1 (6.7)

These responses once again underscore the degree to which DR and DME lead to a reliance on family and friends and other forms of assistance, most commonly for travel to and from appointments.

Travel and Time Commitment

Almost half of the respondents indicating facing travel time of less than 30 minutes (45.5%) to get to their injection appointment, followed by 31 - 60 minutes (40.9%) and 1 - 2 hours (9.1%).

Table 8. Travel time (one-way) to injection appointment (n = 22)

Time	n (%)
Less than 30 minutes	10 (45.5)
31-60 minutes	9 (40.9)
More than 1 hour, and less than 2 hours	2 (9.1)
More than 2 hour, and less than 4 hours	0 (0.0)
4 hours or longer	1 (4.5)

When asked how long they spend at their injection appointments, the larges group reported less than 1 hour (42.9%), followed by 1 - 2 hours (33.3%) and 2 - 4 hours (14.3%).

Table 9. Total time spent per appointment at office of doctor/clinician for injection appointment (n = 21)

Time	n (%)
Less than 1 hour	9 (42.9)
More than 1 hour, and less than 2 hours	7 (33.3)
2 hours or more, but less than 4 hours	3 (14.3)
4 hours or more, but less than 6 hours	1 (4.8)
More than 6 hours	1 (4.8)

In terms of the ease or difficulty of travel, responses were varied but skewed towards the easy end of the spectrum, with most respondents selecting that travel is either very easy (27.3%), easy (27.3%), or neither easy nor difficult (27.3%).

Table 10. What is it like to travel to your injection appointments? (n = 22)

Ease of travel	n (%)
Very difficult	0 (0.0)
Difficult	4 (18.2)
Neither easy nor difficult	6 (27.3)
Easy	6 (27.3)
Very easy	6 (27.3)

That said, 4 individuals did report difficulty related to their travel, and when asked about the reasons, they selected distance from home (50%), poor condition of vehicle (25%), cost (25%), and difficultly related to taking public transit (25%).

Table 11. What makes it difficult for you to travel to your injection appointments (n = 4)

Reason	n (%)
It is far from home	2 (50.0)
My vehicle is in poor condition	1 (25.0)
Poor road conditions	0 (0.0)
It is expensive to travel	1 (25.0)
Other*	1 (25.0)

**Alone it is impossible to take the metro, but with my daughter, difficulty is when I don't hold her arm*

Interestingly, although in these responses both travel and waiting appear as somewhat minimal concerns, both are flagged as the most difficult aspects of the injection routine in data from a different question. When asked what makes it difficult to travel to injection appointments, half of the respondents selected long wait times, while the remainder selected difficulties such as "finding someone to drive me to/from the appointment" (31.8%) and "taking time off work to attend" (27.3%).

Table 12. Most difficult part of eye injection appointments (n = 22)

Reason	n (%)
Anxiety or fear about the injection	6 (27.3)
Long waiting time at the appointment	11 (50.0)
Cost of travel to/from the appointment	0 (0.0)
Finding someone to drive me to/from the appointment	7 (31.8)
Finding someone to help me with my daily tasks after the injection	0 (0.0)
I don't find any part difficult	4 (18.2)
Scratchiness or pain in my eye after the appointment	4 (18.2)
Taking time off work to attend	6 (27.3)
Other*	3 (13.6)

**Spouse must take time off work to drive me, if I didn't have my daughter I'd find difficulties in everything, hotel stay required (travel from Yukon to Vancouver) which is expensive*

When framed or conceptualized in terms of what is most difficult, then, both travel and waiting emerge as central concerns. It is also worth considering whether these issues are exacerbated in rural parts of Canada. Although a regional sub-analysis has not be conducted for this study, it is entirely possible that travel, waiting, and strain on caregivers are even more challenging for Canadians living in rural and remote parts of the country. This is certainly a factor that needs to be considered in the development of new treatments for these diseases.

Emotional and Physical Effects

In response to the question about difficulty, a significant number of patients also selected "anxiety or fear about the injection" (27.3%), highlighting the fact that injections into the eye are emotionally burdensome for some patients. This is interesting, considering that many patients also indicated being "satisfied" with their injections, as well as appreciative of the impact on their sight. It may show that those with DR or DME tend to manage their fear and anxiety in relation to injections as a matter of course. Injections still carry an emotional or psychological impact, but this has become internally managed in such a way as to be common or matter of fact.

The physical burdens of injections are not to ignored either. In response to the same question about the difficult aspects of injections, 18.2% of patients indicated "scratchiness or pain in the back of my eye" as a difficulty worth noting. It is clear that physical impacts are a factor for some patients, then. This is supported to some degree by the number of patients who experience some pain during the injection: when asked to indicate their pain level, a significant majority selected that the injections are "slightly painful" (81.8%). The remainder selected "not painful at all" (9.1%) and "painful" (9.1%).

Table 13. How painful is the injection for you? (n = 22)

Reason	n (%)
Not painful at all	2 (9.1)
Slightly painful	18 (81.8)
Painful	2 (9.1)
Extremely painful	0 (0.0)

Moving into the evening after the injection, our respondents showed an overall transition into a more painful experience. While 45.5% of patients indicated that the evenings are "not painful at all," 40.9% selected "slightly painful" and 13.6% chose "painful." As a result, over half of respondents indicated some form of eye pain lingering into the evening.

Table 14. How painful is the injection for you in the evening after? (n = 22)

Reason	n (%)
Not painful at all	10 (45.5)
Slightly painful	9 (40.9)
Painful	3 (13.6)
Extremely painful	0 (0.0)

Vision was shown to be impacted post-injection as well, with the largest group of respondents selecting that their vision stayed blurry "until I go to sleep that night" (31.6%). This was followed by vision being blurry for 1 - 3 hours (26.3%) and for 4 - 6 hours (21.1%).

Table 15. After an injection, for how long is your vision blurry? (n = 19)

Frequency	n (%)
Less than 1 hour	3 (15.8)
1-3 hours	5 (26.3)
4-6 hours	4 (21.1)
For at least 24 hours	1 (5.3)
Until I go to sleep that night	6 (31.6)

Given the prevalence of blurry vision among the cohort, it is unsurprising that they indicated a number of daily activities that become difficult or impossible post-injection. When asked about which activities they can longer do after an injection, the largest groups chose “watch TV” (57.1%) and “read” (57.1%), followed by “drive” (28.6%), “work” (21.4%), and “prepare meals (14.3%). All respondents to this question choose at least one activity that they can no longer do.

Table 16. Which of the following are you unable to do after an injection? (n = 14)

Activity	n (%)
Watch TV	8 (57.1)
Read	8 (57.1)
Drive	4 (28.6)
Prepare meals	2 (14.3)
Provide care to family members	0 (0.0)
Work	3 (21.4)
None of the above activities	0 (0.0)

These responses emphasize the emotional and physical impacts of living with and treating DR and DME, making it clear that the diseases exact a physical and psychological toll that exists alongside the logistical and financial challenges associated with travel and time.

5. Improved Outcomes

Our survey did not ask patients for their views on improving their experiences and outcomes. That said, the responses to our survey make it clear that any treatment that reduces the physical, psychological, and logistical strain on patients would be preferred. In terms of physical and psychological strain, this could take the form of a treatment that is less invasive, or one that is similarly invasive but that is administered less frequently. The frequency of the treatment could play a role in the reduction of logistical demands as well: a treatment that is taken or received less often would require fewer travel appointment, would decrease dependency on caregivers, and potentially more.

6. Experience With Drug Under Review

As discussed under Section 4, while participants indicated receiving aflibercept as a treatment, it is assumed that this was aflibercept (2mg) and not the drug under review as aflibercept (8mg) was not approved for non-clinical trial use in Canada at the time this survey was completed (2020). We also have no evidence that any of the respondents participated in a clinical trial or had firsthand experience with the drug under review (aflibercept (8mg)).

7. Companion Diagnostic Test

Not applicable.

8. Anything Else?

Researchers, health practitioners, policy experts, and others agree that diabetes is a growing and evolving epidemic, both globally and in Canada. As the incidence of diabetes grow, DR and DME will grow as well. A patient's life is impacted by these diseases through a range of factors: life changes, loss of productivity, missed work/school hours, and more. As our data shows, DR and DME are diseases that weigh heavily on a patient's mind, suggesting a strong psychological burden. Caregivers are impacted by the diseases as well, and in complex ways that are not always easy to measure or quantify.

DR and DME have these impacts, surely, but it is safe to assume that those impacts and associated burdens are more pronounced among vulnerable populations and those living outside of Canada's urban centres including in indigenous populations who face an increase risk of developing type 2 diabetes. And through the COVID pandemic, it is also safe to assume that the burdens and challenges highlighted in patient responses have only become more pronounced. As the number of people living with diabetes in Canada increases, more patients in rural communities will need options that are effective, that help them comply with treatment programs, and that reduce the psychological toll of the disease.

In the context of diabetes, different people with diabetes require different medications and treatment modalities to help them effectively manage their disease. Their unique clinical profile, preferences and tolerance of therapy should direct prescribers to the most appropriate choice and combination of treatments for disease management. Health care providers must be supported in prescribing evidence-based therapies and, through public and private drug plans, patients should have access to a range of treatments that will allow them to optimize their health outcomes. For those paying out-of-pocket, costs should not be so high as to prohibit medication procurement. While current therapies have generally led to improvement for many people with diabetes in blood glucose and hemoglobin A1c control, respondents hope for additional affordable agents that they can access equitably, in a timely manner, and with good result to help them lead a normal life. "X medication" may help people to achieve better glycemic control, which could potentially improve lives and save millions in direct health care costs. For this reason, "X medication" should be an option for people living with diabetes.

This submission is a snapshot of the experiences of a small number of DR and DME patients in Canada—not a complete or final one, of course, because no overview can be, but nevertheless one that is grounded in the lived experiences of patients who offered their time, expertise, and insights to participate in this process. The focus of this submission has been on expanding our understanding of how these individuals perceive their diseases and treatments; the burdens that impact their lives; the barriers they face as a result of vision loss and other factors; and the psychological and emotional tolls of the diseases. As organizations that represent patients with DR, DME, and other eye diseases, our overarching goal is to contribute meaningfully to the discussion and potential implementation of new treatments in this space—in particular, to guide that discussion along lines that are patient-centered, that focus on optimal and equitable outcomes, and that recognize the expertise of patients with lived experience of DR/DME and their value in the review process of new treatments.

We look forward to continuing to work with CADTH to support Canadians living with DR and DME, and to advance our collective understanding of how the diseases impact their lives.

Appendix: Patient Group Conflict of Interest Declaration

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.
    - FBC contracted Dr. Chad Andrews as an independent consultant with expertise in patient centered research to draft this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.
    - FBC contracted JRL Research & Consulting to program and test the survey, perform qualitative interviews and clean and analyze the data.
3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer				X
Novartis				X
Roche				X
Abbvie-Allergan				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Larissa Moniz
Position: Director, Research and Mission Programs
Patient Group: Fighting Blindness Canada
Date: July 14, 2023

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer				X
Novartis				X

Abbvie				X
Roche				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jim Prowse
Position: Executive Director
Patient Group: The Canadian Council of the Blind
Date: July 18, 2023

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer (CNIB)				X
Johnson & Johnson (CNIB)			X	
Novartis (CNIB)		X		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Thomas Simpson
Position: Executive Director, Public Affairs and Come to Work
Patient Group: CNIB
Date: August 18, 2023

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None to Declare				

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jennifer Urosevic
Position: President and CEO
Patient Group: Vision Loss Rehabilitation Canada
Date: August 22, 2023

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Novo Nordisk				X
AstraZeneca	X			
Janssen			X	

Sanofi	X			
Bayer	X			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Laura Hoffe
Position: Senior Manager, Policy
Patient Group: Diabetes Canada
Date: August 3, 2023

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer				X
Abbvie			X	
Pfizer Canada				X
Sanofi Canada				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jane Barratt
Position: Secretary General
Patient Group: International Federation on Ageing
Date: 4th August 2023

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0813-000
Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL
Indication: For the treatment of diabetic macular edema (DME)
Name of Clinician Group: Southwestern Ontario Community Ophthalmologists
Author of Submission: Dr. Jaspreet Rayat

1. About Your Clinician Group

This clinician group is comprised of 4 practicing ophthalmologists with community practices in Southwestern Ontario: Dr. Richard Weinstein, Dr. Jaspreet Rayat, and Dr. Carl Shen (all from Ocular Health Centre in Kitchener - https://www.ocularhealthcentre.ca/); Dr. Murari Patodia from Sarnia (Patodia Eye Institute - https://www.patodiaeyeinstitute.com/).

Our group's purpose is to support the continuous improvement of outcomes and optimal management of patients with retinal diseases.

2. Information Gathering

Our group, excluding Dr. Shen, met virtually for 1 hour on August 22nd with the support of a medical writer to capture our opinions. Dr. Shen reviewed a draft of this input template and provided his support for the recommendations via email. Subsequent review and refinement of the final input template was completed via email.

3. Current Treatments and Treatment Goals

The current Canadian treatment landscape for DME in Canada is comprised mainly of anti-vascular endothelial growth factor (VEGF) treatments administered as intravitreal injections into the eye. Therapeutic options are as follows:

- Aflibercept (EYLEA®) (2 mg/0.05 mL)
- Ranibizumab (LUCENTIS®)
- Ranibizumab (biosimilar – BYOOVIZ™)
- Brolucizumab (BEOVU®)
- Faricimab (VABYSMO®)
- Bevacizumab (AVASTIN®) – **off-label for use in intraocular injections**

Bevacizumab is poorly accessible for patients over 65 (i.e. key age demographic for DME), requiring out of pocket payment in Ontario as it is not on the formulary, and brolucizumab is not favoured by physicians due to associated risks of intraocular side effects.

Additional treatments for DME include laser therapy and corticosteroid injections. However, risk of retinal scarring with laser therapy and adverse events associated with corticosteroid injections (risk of cataract formation, increased ocular pressure) often preclude their use and reinforce preference for anti-VEGF treatments listed above. Additionally, intravitreal steroid injection medications are not covered for any age bracket, which is a hinderance to accessibility and financial burden as they also require repeated treatment.

Current treatments target the disease state, helping to slow, stop and sometimes even reverse disease progression. Treatments have the dual benefit of treating disease symptoms by helping to stabilize vision. Despite this, these treatments are not curative; the main treatment goal is therefore to maintain vision while extending the duration between treatments to reduce the treatment burden (given their invasive nature). A treatment such as aflibercept 8 mg/0.07 mL which is as efficacious as, but less frequent than, the current standard of care satisfies this need.

The value of reducing injection (treatment) burden is broad and impactful, including the associated reduction of:

- Direct and indirect costs (injection fees, clinic visits, time off work for patient or caregiver to obtain injections)
- Overall cost to healthcare system
- Patient discomfort
- Risks associated with intravitreal injections, albeit rare (endophthalmitis [i.e. infection], eye hemorrhage, lens perturbation leading to cataract, and retinal detachment)
- Patient inconvenience
- Caregiver burden (patients with poor vision require a driver; patients may be of older age and require transportation by a caregiver)

Reduced time spent on injections at clinic visits also allows for greater focus on other areas of ocular health, thus potentially helping to reduce the burden of other ocular conditions.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Given the key treatment goal of maintaining vision while extending the duration between treatments, there are currently no available drugs which can reliably extend patients to longer durations to minimize treatment burden. Existing treatments were designed and studied to be used only at the more frequent, indicated interval (i.e. ~every 2 months). A treatment formulation designed and studied with an extended dosing interval would help address this unmet need. Reduced treatment burden and greater convenience for patients would also help promote treatment compliance.

Aflibercept 8 mg/0.07 mL was studied specifically with extended treatment intervals in the PHOTON Trial and thus is the only treatment with robust evidence supporting extended dosing intervals. Indeed, instead of every two months, 89% of patients receiving 8 mg aflibercept were on a ≥12-week dosing interval after two years. This interval could potentially be extended even further than currently done for those with low disease activity receiving 2 mg aflibercept, based on physician discretion.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Given greater duration of effect, aflibercept 8 mg/0.07 mL is expected to replace use of the 2 mg/0.05 mL formulation, thus establishing 8 mg/0.07 mL aflibercept as the new first-line treatment of choice for this disease.

We anticipate patients currently receiving 2 mg/0.05 mL aflibercept will be switched to the 8 mg/0.07 mL formulation, assuming adverse events such as increased intraocular pressure from the higher volume/concentration remain low.

Aflibercept 8 mg/0.07 mL may also be considered an alternative to BYOOVIZ™, for physicians with concerns of reduced efficacy of biosimilars.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients with this disease requiring treatment with an anti-VEGF therapy would be suitable for this treatment.

A monocular patient (affected by disease in only one eye), may be slightly less suitable until a pre-filled syringe formulation is available due to potential risk of infection if vial is not designed for multi-use.

Diagnosis of this disease, via vision assessment and clinician examination of the eye, is well-standardized – misdiagnosis and underdiagnosis are rare.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Response to treatment is determined by the stabilization of vision and anatomical outcomes. Eye anatomy is measured via optical coherence tomography (OCT) scan to assess the thickness of the retina and the presence of fluid. Response assessment is highly standardized and the same in clinical practice as in trials. The outcomes are “binary” (i.e. the drug works or does not) and are thus not subject to variable interpretation.

Ophthalmologists use the treat-and-extend dosing strategy, which incrementally increases the dosing interval based on patient response to the drug (i.e. as long as retina remains dry and stable – assessed via OCT). This approach will not change with the introduction of aflibercept 8 mg/0.07 mL, but it will allow for longer durations between injections.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The factors impacting the decision to discontinue aflibercept 8 mg/0.07 mL will be the same as for the 2 mg/0.05 mL aflibercept formulation.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Aflibercept 8 mg/0.07 mL will be used only by physicians who are specialized in ophthalmology, who are equipped to assess and manage this disease, as well as address adverse events. Aflibercept 8 mg/0.07 mL will be primarily administered in the ophthalmologist’s office but may rarely be given at hospital outpatient clinics.

6. Additional Information

Given existing physician comfort with the efficacy and safety profile of the aflibercept molecule, the 8 mg/0.07 mL dose will fit seamlessly into ophthalmologists’ treatment arsenal, more so than other new therapies with less experience.

While there currently are not considerable wait times for injections, demographic trends suggest that the prevalence of DME is likely to rise. This would lead to an increased demand for ophthalmologist-based injections which could not be met, with resulting delays in treatment. However, reduced injection frequency facilitated by aflibercept 8 mg/0.07 mL would be very valuable in addressing this potential increased demand.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

Yes. A third-party (non-pharmaceutical company) communications agency was used to manage logistics and record clinician group input.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Jaspreet S Rayat
Position: Assistant Clinical Professor Adjunct, McMaster University, Co-Owner of Ocular Health Centre
Date: 24-08-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer	X			
Novartis	X			
Bausch + Lomb	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Richard Weinstein M.D.
Position: Ophthalmologist, Co-founder of Ocular Health Centre
Date: 28-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Bayer	X			
Novartis	X			
Bausch + Lomb	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Murari Patodia
Position: Ophthalmologist in private practice
Date: 24-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
Bayer	X			
Allergan	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Carl Shen
Position: Physician
Date: 24-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
N/A – no COI to declare				

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0813-000
Generic Drug Name (Brand Name): Aflibercept 8mg
Indication: Diabetic Macular Edema
Name of Clinician Group: Canadian Retina Society
Author of Submission: Varun Chaudhary

1. About Your Clinician Group

The Canadian Retina Society (CRS) represents the Ophthalmologists in Canada whose primary area of patient care is surgical and/or medical vitreoretinal disease. The CRS website is www.crsscr.ca.

2. Information Gathering.

Literature review, Systematic reviews and meta-analyses and podium presentations at scientific meetings.

3. Current Treatments and Treatment Goals

In Canada, the estimated prevalence of diabetic macular edema in 15.7% in patients with diabetes. The prevalence of visual impairment due to DME is 2.6% [R.J.Petrella et al, Journal of Ophthlamology, vol 2012]. As a result, diabetic retinopathy remains the second most common cause of severe vision loss in Canada. Composite scores for vision-related quality of life declined with increase visual acuity loss in a study of 145 Canadian patients with DME [Gonder J et al, Journal of Ophthalmology, vol 2014].

The recommended standard for treatment of center-involving DME (CI-DME) is anti-vascular endothelial growth factor (anti-VEGF) agents that are delivered by intravitreal injection. A Cochrane network meta-analysis of randomized controlled trials (RCTs) evaluating patients with DME (n= 6007 patients) demonstrated anti-VEGF agents were more effective than previous standard of care (laser) for improving vision after one year with high-certainty evidence (Virgili G et al, Cochrane Database Syst Rev. 2018;(10)) Risk Ratio (RR) for vision gain for aflibercept versus laser was 3.66 (95% CI 2.79 to 4.79), RR for bevacizumab versus laser was 2.47 (95% CI 1.81 to 3.37) and RR for ranibizumab versus laser was 2.76 (95% CI 2.12 to 3.59). As such, clinically anti-VEGF therapy has become the standard of care for treatment of DME. As per the evidence in the literature, anti-VEGF treatment are the 1st line of treatment for CI-DME across Canada.

The current anti-VEGF treatments do modify the underlying disease mechanism. This is supported by regression in Diabetic Retinopathy Severity Score (DRSS) with anti-VEGF treatment (RISE, RIDE, VIVID, VISTA trials). In addition, there is evidence that anti-VEGF treatment can slow progression of retinal non-perfusion (RECOVERY trial / post-hoc analysis of RISE/RIDE and VISTA trials).

However, treatment and monitoring burden remains a key clinical challenge for Canadian patients undergoing treatment for DME. Protocol I from DRCR.net is the clinical trial that provides us guidance on long term treatment need and monitoring. Although the number of treatments decrease significantly after year 2, to achieve optimal outcomes, patient required a median number of 13 clinic appointments in year 1, 10 appts in year 2, 8 appts in year 3, 6 appts in year 4 and 5 appts in year 5. This high frequency of close monitoring is required with 1st generation anti-VEGF agents that have limited durability. However, this frequency of monitoring is not feasible in real world clinical practice.

One important unmet need in DME treatment paradigm is durability. Reducing treatment burden and allowing for a fluid free retina for longer duration allows for maintenance of maximal vision gains over the lifetime of the patients This translates into improved quality of life, increased independence, reduce risk of falls, reduced depression and a myriad of other improved quality of life metrics that have been associated with vision loss secondary to DME in the literature over the past many decades. In addition, safety is vital to ensure minimal risk of ocular complications. Ocular inflammation is an important side effect that can compromise visual outcomes for patients. Newer agents with increased durability and a robust safety profile will be vital to improve long term outcomes for Canadians living with DME. By reducing the number of injections required, a more durable agent will limit the patient's exposure to the rare but devastating risks associated with intravitreal injections (such as endophthalmitis).

DME is a multi-factorial disease with complex interplay of a myriad to intraocular cytokines. Personalized care will necessitate that durable agents with different mechanism of action are available to Canadian patients. Newer treatments that reduce treatment and monitoring burden will be critical to enhance the patient journey and optimize outcomes for Canadians living with DME. Recently approval of Faricimab is an important step forward as this agent has demonstrated long durability in DME management. Other durable agents with different mechanism of action will further provide opportunity to personalize care for patients while reducing treatment and monitoring burden.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Treatment Burden: First generation anti-VEGF agents (Ranibizumab, Aflibercept 2mg) were tested in phase 3 pivotal RCTs involving eyes with DME and achieved statistically significant, and clinically important, vision gains with at least one treatment group receiving regular fixed intravitreal injections of anti-VEGF agents. These protocols included giving anti-VEGF agents monthly (every 4 weeks) or every 2 months (every 8 weeks) for 2 years; however, fixed dosing regimens can be burdensome for patients and physicians, as well as the healthcare system and in most situations result in overtreatment. Evidence from RCTs may also not be generalizable to routine clinical practice due to high treatment and monitoring standards resulting in under-treatment and under-monitoring in the real-world.4 This has led to a gap between real world outcomes and pivotal clinical trial results, and resulted in Canadian patients experiencing less than expected visual improvement with the current agens.

Next generation agents are attempting to optimize durability while achieving optimal vision outcomes. Faricimab was recently approved by Health Canada and has demonstrated significantly enhanced durability. Approximately 65% of patients were on q16 week dosing at week 96 compared to q8week dosing with gold standard fixed dosing with aflibercept. The mean number of injection in year 2 for the personalized treatment arm was 3 injections which is a significant reduction in treatment burden and monitoring burden compared to current standard of care.

Data from clinical trials with High Dose Aflibercept has demonstrated that this next generation anti-VEGF agent with a different MOA than Faricimab can also provide optimal vision outcomes while significantly reducing treatment and monitoring burden. Data from the Pivotal Phase 3 DME PHOTON trial demonstrated that Mean number of injections over 96 weeks in the q16 week group was 7.8. In addition 89% of patient maintained dosing intervals >/= to 12 weeks. Another key durability signal was that 44% of 8mg patients

had as assigned dosing interval of >/= 20 weeks at Week 96. This durability is the longest durability signal that has been tested and achieved in any phase 3 pivotal DME treatment program with anti-VEGF agents and will be of high clinical importance for management of patients with DME in Canada.

Long Term Outcomes: Anti-VEGF agents in DME are very effective at improving vision during an intense loading phase of typically month injections given for 3-6 months in most clinical trials. Maintaining these vision gain over the following years has been challenging. In the context of a clinical trial setting and very regular monitoring and treatment schedule, DRCRnet Protocol T demonstrated that patients had gained on average 2 lines of vision from baseline to month 24. However, during the extension phase of the study, from year to 3 to 5, patients lost 1 line of vision likely secondary to reduced monitoring and treatment frequency. This loss of vision in extension studies has been seen across the board including open label extension studies from RISE and RIDE trials. Moreover, all these studies have demonstrated other markers for under treatment including regression of Diabetic Retinopathy Severity Score which suggests that in addition to functional vision outcomes, important anatomic outcomes also demonstrate a negative trend in long term follow-up. Therapeutics that reduce treatment and monitoring burden will be vital to help mitigate the long-term vision loss in DME. Data from PHOTON study demonstrated that even with reduced loading dose with 3 monthly treatment with High Dose Aflibercept compared to 5 monthly doses with Aflibercept 2mg (control), optimal disease control could be achieved in terms of reduction in fluid on OCT and this was maintained out to week 96 in the q16 arm compared to the q8 control arm. Achieving optimal anatomical results with reduction in treatment frequency will be important to achieve optimal long term outcomes for Canadian patients living with DME.

c) Safety: Newer agents including brolucizumab have demonstrated increased durability than previous agents. However, the safety profile of brolucizumab has been a limiting factor due to concerns regarding inflammation and occlusive retinal vasculitis. As such, newer agents must not only be more durable, but also demonstrate high safety profile that is in line with the currently used drugs. PHOTON trial has not demonstrated any new safety signal for High Dose Aflibercept compared to control arm with Aflibercept 2mg. Of note there were no cases of retinal vasculitis reported.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

This agent builds on our current treatment strategy. In terms of new generation, more durable agents, Faricimab is the only approved agent in Canada. High Dose Aflibercept 8mg has a different mechanism of action than Faricimab. High Dose Aflibercept 8mg is a fully human recombinant fusion protein that binds VEGF-A, VEGF-B and PIGF, thereby inhibiting the activation of cognate VEGF receptors. In terms of next generation anti-VEGF agents with a stronger durability signal, High Dose Aflibercept 8mg is unique and different in that it builds on the 10 plus year of clinical experience with Aflibercept 2mg, however provides a much higher dose with different pharmacokinetics.

This agent has demonstrated non-inferior vision results with less frequent treatments compared to the current gold standard treatment in head-to-head Phase III pivotal trial. As such, this agent can be considered as first-line treatment or as rescue treatment for patients not responding well to current drugs that are available for DME treatment.

The durability for this agent will allow clinicians the confidence to extend patients longer between treatments than our current gold standard. That reduction in treatment burden will be an important paradigm shift.

Very importantly, High Dose Aflibercept 8mg in the PHOTON trial tested and provided robust evidence for a paradigm shift in how DME care can be managed. This trial demonstrated that early rapid extensions immediately after 3 monthly loading doses with High Dose Aflibercept 8mg can significantly reduced treatment and monitoring burden even in year 1. Despite early and rapid extensions to q12 or q16 weeks, patients achieved non-inferior visual acuity and anatomic outcomes compared to historic gold standard Aflibercept 2mg fixed dosing. This Treat and Reduce type treatment algorithm that has been tested with High Dose Aflibercept has a potential to dramatically change the treatment paradigm with a reduction in monitoring and treatment visits early in the treatment course for Canadian patients.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients in Canada with DME will benefit from a safe and durable therapeutic agent similar to the one under review. New patients will benefit from effective disease control and reduced burden. Patients currently under treatment could potentially reduce their treatment burden and reduce the number of monitoring and treatment visits by switching to a newer, more durable agent.

This drug will help address many of the key unmet needs for Canadians living with DME.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Subjective outcomes – Visual acuity test

Objective Outcomes – Fluid on OCT testing

Clinical exam – Presence of macular thickening on exam

Treatment response should be assessed at each scheduled follow-up appointment as clinically indicated or sooner if patient has a change in vision.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

End stage disease with significant atrophy and/or fibrosis and no improvement despite regular treatments.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Ophthalmology offices in the community and in hospital settings where treatment is provided by physicians experienced in diagnosing and monitoring for treatment response and potential complications. Physicians should also be experienced in providing intravitreal therapy for retinal diseases.

6. Additional Information

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Varun Chaudhary
Position: President, Canadian Retina Society
Date: 27-08-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer		X		
Roche		X		
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Bernard Hurley
Position: Vitreo-retinal surgeon, The Ottawa Hospital, and Fellowship Director, the University of Ottawa Eye Institute
Date: 27-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Allergan	X			
Novartis	X			
Alcon Canada	X			
Bayer	X			
Roche	X			
Biogen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Amin Kherani
Position: Clinical Associate Professor, Department of Surgery, Faculty of Medicine, University of Calgary
Date: 31-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Bayer		X		
Bausch + Lomb	X			
Roche	X			
Apellis		X		
Novartis	X			
Alcon	X			
Allergan	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Cynthia Qian
Position: Clinical Assistant Professor, Université de Montréal, Hôpital Maisonneuve-Rosemont, Vitreo-Retinal Surgeon, Montréal, Québec
Date: 31-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie	X			
Apellis	X			
Boehringer Ingelheim	X			
Bayer		X		
Novartis		X		
Roche		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0813-000
Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL
Indication: For the treatment of diabetic macular edema (DME)
Name of Clinician Group: Northeastern Ontario Ophthalmology Group
Author of Submission: Dr. Stephen Kosar

1. About Your Clinician Group

Our group is composed of 3 ophthalmologists practicing in Northeastern Ontario:

- North Bay (https://www.esno.ca/about-esno/doctors/): Dr. Vanessa Ellies
- Timmins: Dr. Alejandro Oliver
- Sudbury: Dr. Stephen Kosar

2. Information Gathering

The information was gathered through email. A medical writer supported by placing information gathered into the Clinician Input Template.

3. Current Treatments and Treatment Goals

Current treatments for DME used in Canada include Eylea (Aflibercept), Lucentis (Ranibizumab), Beovu (Brolucizumab), Vabysmo (Faricimab) and Avastin (Bevacizumab).

The main goals of treatment are to stabilize disease (i.e. prevent worsening) and hopefully improve vision as well as patient quality of life.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There is an excessive burden providing injections for both AMD and DME in underserviced areas of Northern Ontario. Post-COVID there are also issues with staffing and an inability to provide timely services to these patients.

The 8 mg dose of Aflibercept can potentially reduce the number of injections by increasing the dosing intervals.

Phase 3 studies using the 8 mg dose showed evidence for extending dosing intervals to every 16 weeks and beyond through two years of study.

Phase 3 studies using the 8 mg dose also showed evidence that patients treated every 16 weeks received 4.6-6 fewer injections compared with the 2 mg dose every 8 weeks with no significant differences in visual acuity increases.

Therefore, reducing the frequency of dosing using the 8 mg dose without sacrificing vision is important for patient care.

It reduces the number of treatments for patients. This can reduce the number of trips to the doctor's office. This is very important in Northern Ontario because of the long distances to treatment centres and issues with winter weather and road conditions.

Reduced number of patient injections also frees up more time for the limited number of ophthalmologists in Northern Ontario to see more affected patients.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Assuming cost equivalency, Aflibercept 8 mg could be used as a first-line treatment in patients where an extended treatment interval is desired. Aflibercept 8 mg could also be used in second-line, either for those who desire a longer treatment interval than their current therapy or for where first-line treatment with another agent has failed.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Aflibercept 8 mg would be suitable for all patients. This treatment is **especially valuable** for the following patient groups:

- Elderly
- Infirm
- Mobility issues/difficulty travelling
- Institutionalized
- Remote locations/long distances from treatment centres (especially in winter)

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The outcomes used to determine treatment response are the same as currently used: optical coherence tomography (OCT) scan and clinical examination (to assess visual acuity and the retina). Given these measures are required at each visit to determine whether the treatment interval can be modified, a longer-acting treatment such as Aflibercept 8 mg would offer cost benefits to the healthcare system by reducing the number of OCT scans and patient visits.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The factors impacting the decision to discontinue treatment with Aflibercept 8 mg will be the same as used with currently available therapies and are dependent on individual clinical scenarios.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Aflibercept 8 mg will be administered mostly in ophthalmologist offices, and occasionally in hospital-based clinics (such as teaching institutions). While this treatment will be administered predominantly by retinal specialists, general ophthalmologists may also administer Aflibercept 8 mg in regions where retinal specialists are lacking. General ophthalmologists administering the injections may do so independently or under the guidance of a retinal specialist.

6. Additional Information

CADTH should already be aware of the following pivotal studies:

- Two-year PULSAR Trial Results for Aflibercept 8 mg Demonstrate Durable Vision Gains at Extended Dosing Intervals in Wet Age-related Macular Degeneration | Regeneron Pharmaceuticals Inc.

- Aflibercept 8 mg Two-Year Results from Pivotal PHOTON Trial in Diabetic Macular Edema Presented at ASRS | Regeneron Pharmaceuticals Inc.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Yes. A medical writer supported by placing information gathered into the Clinician Input Template.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Stephen Kosar
Position: Ophthalmologist
Date: 30-08-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer	X			
Novartis	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Alejandro Oliver
Position: Assistant Professor of Ophthalmology
Date: 30-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
Bayer	X			
Viatris	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Vanessa Ellies
Position: Ophthalmologist
Date: 31-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0813-000
Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL
Indication: For the treatment of diabetic macular edema (DME)
Name of Clinician Group: Retina Division of the Ottawa Hospital
Author of Submission: Dr. David Maberley

1. About Your Clinician Group

Our group includes three ophthalmologists from the Retina Division of The Ottawa Hospital: Dr. David Maberley, Dr. Michael Dollin, and Dr. John Adam McLaughlin. Our purpose is to provide optimal care for patients with retinal diseases.

2. Information Gathering

Information in this submission was gathered via phone and email, with the support of a medical writer to record input.

3. Current Treatments and Treatment Goals

Three treatments are currently used for this disease area:

- Aflibercept - injections every one-two months
- Ranibizumab - injections every month
- Bevacizumab (off-label) - often requires more frequent injections and up-dosing (especially for DME)

A longer-acting therapy, brolucizumab, was approved by Health Canada, but safety concerns have led to the avoidance of this treatment.

The main goal of treatment is to improve quality of life by improving or stabilizing visual acuity. There are also many secondary benefits to improved/stabilized vision including:

- Reduced falls
- Positive cognitive impact (i.e. those with vision loss are more susceptible to depression and dementia)
- Increased ability to drive (especially for younger patients with DME), allowing for socialization and holding employment
- Reduced ocular treatment burden in patients with DME who may already have a high medical burden (e.g. managing kidney disease)

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Currently, all approved treatments require frequent injections into the eye (~every 1-2 months). There is a great unmet need for longer-acting therapies. Longer-acting therapies allow for a reduced frequency of injections which translates to:

- Reduced risks related to injection
- Less time required for patients/caregivers to attend appointments

- Cost advantage for payers from fewer treatments needed
- Reduced cost from fewer physician visits
- Additional time in ophthalmologists' schedules to treat other ocular issues (which are currently at maximum capacity)

Aflibercept 8 mg certainly meets this unmet need, with the results of the PHOTON trial showing 89% of patients remained on the ≥12 week interval at 2 years.

We also strive to provide the safest treatments possible to patients. Given our extensive experience with aflibercept, we are comfortable that this is a safe treatment. The known safety profile of aflibercept will facilitate more rapid uptake of aflibercept 8 mg compared to a new treatment of an unknown molecule.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Givin its greater duration, we expect aflibercept 8 mg will replace aflibercept 2 mg as a first-line treatment option (assuming cost equivalency). Aflibercept 8 mg could also be used as a second-line treatment option for patients who fail other anti-vascular endothelial growth factor (VEGF) treatments.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Aflibercept 8 mg would be suitable for virtually all patients, except possibly for those who experience intraocular pressure following intravitreal injections, which may be a risk from injection of a larger volume (0.07 ml with aflibercept 8 mg vs. 0.05 ml with aflibercept 2 mg).

There are no notable issues related to diagnosis in this area, and diagnosis paradigms would not change for aflibercept 8 mg.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Response assessment with aflibercept 8 mg will remain the same as for currently approved therapies.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The factors considered when discontinuing treatment (i.e. switching to another anti-VEGF therapy) are unchanged with aflibercept 8 mg.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Aflibercept 8 mg will be administered by ophthalmologists in hospitals or private clinics.

6. Additional Information

N/A

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation.

Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Yes, a medical writer recorded our input.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   N/A

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. David Maberley
Position: Head, Department of Ophthalmology, The Ottawa Hospital
Date: 30-08-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Alcon	X			
Apellis	X			
Bayer	X			
Roche	X			
Novartis	X			
Novo Nordisk	X			
Preceyes	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Michael Dollin
Position: Ophthalmologist
Date: 31-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
Bayer	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: John Adam McLaughlin, MD, JD, FRCSC
Position: Assistant Professor, Department of Ophthalmology, University of Ottawa Eye Institute/Retina Centre of Ottawa
Date: 31-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche	X			
Bayer	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0813-000
Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL
Indication: For the treatment of diabetic macular edema (DME)
Name of Clinician Group: Toronto Ophthalmologists
Author of Submission: Dr. Peng Yan

1. About Your Clinician Group

We are a group of both community and academic-based ophthalmologists practicing in Toronto. Our group includes:

- Dr. Peng Yan (Kensington Health - https://www.uhn.ca/Krembil/DKJ-Eye-Institute/Pages/meet-our-team.aspx)
- Dr. Sohel Somani (Uptown Eye Specialists - https://uptowneye.uvisiongroup.com/)
- Dr. Efrem Mandelcorn (University Health Network - https://www.uhn.ca/Krembil/DKJ-Eye-Institute/Pages/meet-our-team.aspx)

Our purpose is to support access to safe, efficacious and tolerable treatment options for patients.

2. Information Gathering

Our group met virtually over Zoom on August 23rd for 1 hour to discuss the submission. A medical writer captured our discussion. The submission was then circulated via email for final approval.

3. Current Treatments and Treatment Goals

Aflibercept 2 mg/0.05 mL is used predominantly as the “gold standard” treatment of choice for DME in Canada. Additional anti-vascular endothelial growth factor (VEGF) treatments are available; Faricimab is a newer treatment option with comparable safety to aflibercept. Brolucizumab is approved and reimbursed for this indication but is used infrequently by ophthalmologists due to its risk of intraocular inflammation. Bevacizumab may be used off-label, but this is very infrequent in Ontario due to lack of coverage/access.

Corticosteroids and laser therapy may be used in patients with DME who are refractory to anti-VEGF treatments.

The main goal of treatment is to maintain vision and prevent vision loss.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Anti-VEGF treatments are administered as intravitreal injections. While the standard dosing is ~every 2 months, some patients may require dosing as frequently as monthly. This can be particularly burdensome for patients, considering the invasive nature of administration, as well as the inconvenience of frequent clinic visits. Furthermore, most patients are of advanced age and require transportation by a caregiver. Frequent injections are therefore associated with poorer patient compliance and may cause patients to be lost to follow-up.

Aflibercept 8 mg offers increased duration between treatment intervals, decreased injection burden and is uniquely supported by a clinical trial. In addition to potentially promoting compliance, reduced injection burden can reduce the burden on patients/caregivers as well as physicians/clinics. Fewer injections also reduce the risk of injection-related complications (although rare). Aflibercept 8 mg is also not associated with the considerable adverse events observed with the already reimbursed brolucizumab. Combined, these benefits translate to a major financial advantage in terms of healthcare costs.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

We anticipate aflibercept 8 mg will become the drug of choice for treatment-naïve patients and share the position of first-line treatment choice with aflibercept 2 mg. Although no head-to-head trials are available, we hypothesize that aflibercept 8 mg is a comparable option to faricimab.

Aflibercept 8 mg would be an alternative for patients currently on aflibercept 2 mg who desire a longer treatment interval. However, if a patient is already receiving anti-VEGF treatment at a longer interval (e.g. every 3-4 months) with no safety issues, they would not likely be switched to aflibercept 8 mg. There is also potential for aflibercept 8 mg to be attempted in previous patients who respond sub-optimally to aflibercept 2 mg.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients indicated for anti-VEGF therapies would be suitable for aflibercept 8 mg. Diagnosis of this disease is clear and the occurrence of misdiagnosis/underdiagnosis is no more likely with aflibercept 8 mg than currently.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Although patient management is nuanced and adapted based on individual patients, the approach to assessing outcomes is generally the same between clinical trials and practice. Response is evaluated by measuring vision status and anatomical changes. Ophthalmologists use the “treat and extend” approach to determine whether to increase the dosing interval. Physicians may be more cautious in extending the interval in practice compared to clinical trials. Overall, aflibercept 8 mg will not change this “treat and extend” approach.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Given the well-known and favourable safety profile of aflibercept, as well as its efficacy in the management of DME, treatment is not generally discontinued but rather injections are increased in frequency until the maximum reimbursed interval (i.e. every 4 weeks) is reached. If the patient continues to have a poor response, the treatment would be switched to another anti-VEGF agent.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Aflibercept 8 mg would be administered predominantly by retina specialists but may also be offered by community-based general ophthalmologists in regions where retina specialists are absent. All injections are performed in the outpatient setting (clinics or hospital outpatient centres).

6. Additional Information

The existing familiarity/comfort with aflibercept is the major driver of anticipated aflibercept 8 mg uptake. We understand this molecule’s efficacy and tolerability profile and are excited to have a formulation which can reduce treatment burden.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Yes, we received support from a medical writer to schedule our meeting and document discussion.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   N/A

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Peng Yan
Position: Ophthalmologist, VitreoRetinal Surgeon
Date: 25-08-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis	X			
Bayer	X			
AbbVie	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Sohel Somani

Position: Ophthalmologist, Medical Retina
Date: 24-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
Bayer	X			
AbbVie	X			
Ripple Therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Efrem Mandelcorn
Position: Ophthalmologist-in-Chief, Department of Ophthalmology, University Health Network
Date: 24-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	X			
Bayer	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0813-000
Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL
Indication: For the treatment of diabetic macular edema (DME)
Name of Clinician Group: Toronto Retina Institute
Author of Submission: Dr. Alan Berger

1. About Your Clinician Group

Our group consists of 3 ophthalmologists from the Toronto Retina Institute (https://www.torontoretinainstitute.com/#/): Dr. Alan Berger, Dr. Shaheer Aboobaker, and Dr. Keyvan Koushan.

The Toronto Retina Institute strives to support patients with retinal diseases through full-spectrum care.

2. Information Gathering

Our input was compiled through telephone and email, with the support of a medical writer to record discussion.

3. Current Treatments and Treatment Goals

Current Canadian treatments for DME include aflibercept (EYLEA®), ranibizumab (LUCENTIS®), faricimab (VABYSMO®), and brolucizumab (BEOVU®). All are approved by Health Canada and have been shown to be efficacious and well-tolerated, apart from some safety concerns with brolucizumab. These treatments target the underlying disease mechanism by impacting the growth of blood vessels and leakage of fluid in the eye. Aflibercept (2 mg) is the most frequently used option for treatment-naïve patients.

Bevacizumab (AVASTIN®) may also be used off-label (not approved for DME). However, clinical trials have demonstrated superiority of aflibercept and ranibizumab over bevacizumab for DME, so bevacizumab would not be used as a first-line treatment. Bevacizumab would typically only be used in patients who do not have insurance and where maximal efficacy is not essential, as it is considerably less expensive if paying out of pocket than currently approved treatments.

While treatments would ideally improve vision, the extent and duration of damage to the retina may impact the ability to achieve improvement. Thus, the main goals of treatment are to improve retinal anatomy and achieve stabilization or improvement in visual acuity.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Treatments for DME are not curative; treatment is therefore ongoing and requires repeat visits with trained clinicians to receive injections into the eye. In addition to the burden on ophthalmology clinics and the healthcare system, this burden extends to patients and caregivers, causing inconvenience and the need to take time off work for appointments. While proper education and positive experience helps promote patient compliance, the notion of receiving frequent injections into the eye for years can be quite onerous

for patients. Indeed, ~75% of patients require injections of their treatments every 8 weeks or less.

Considering the aging population, the incidence of DME and demand for these treatments is expected to rise. The limited number of retinal specialists who can administer these treatments will not sufficiently meet the demand.

These factors highlight the need for a treatment which is as efficacious but more durable/long-lasting than current therapies. Aflibercept 8 mg satisfies this need, given its clinical trials demonstrated equivalent efficacy to aflibercept 2 mg, but with considerably longer intervals between injections required.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Currently, aflibercept 2 mg (EYLEA®) is the most common first-line treatment choice for patients who have financial coverage. We expect aflibercept 8 mg would rapidly replace the 2 mg dose, becoming the new preferred first-line agent and standard of care. Given the longer dosing interval, aflibercept 8 mg may also be chosen preferentially over ranibizumab for first-line treatment. It is unlikely patients who are already on treatment at a convenient and less frequent dosing interval would be switched to aflibercept 8 mg, to avoid perturbing disease control.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All patients eligible for treatment would be suitable for aflibercept 8 mg. While misdiagnosis may rarely occur in clinical practice, diagnostic paradigms will not be impacted by the introduction of aflibercept 8 mg.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Response assessment is the same in clinical practice as in trials and includes the return to both normal anatomy (i.e. decrease in excessive retinal thickness or fluid accumulation) and visual acuity.

Clinicians utilize the treat-and-extend protocol to determine if the interval between treatments can be increased. Interval extension is performed more readily for patients with DME compared to nAMD due to lower risk of permanent damage should disease return.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

The decision to discontinue aflibercept 8 mg is the same as with other currently available treatments. No response or the presence of irreversible macular damage would lead to discontinuation, or a switch in regimen, given the risks (although small) associated with each injection.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Aflibercept 8 mg can be administered in any outpatient office setting (i.e. does not require an operating room), and should preferably be administered by fellowship-trained retinal specialists.

6. Additional Information

Decades of experience with aflibercept support its use as a safe and efficacious treatment. Our comfort with this treatment, combined with the added benefit of additional durability to reduce the frequency of injections is a major advancement in DME treatment.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   We were supported by a medical writer to record discussion and organize clinician input.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   N/A

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Alan R Berger
Position: President and Co-founder: Toronto Retina Institute
Date: 26-08-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Bayer Canada	X			
Roche Canada	X			
Biogen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Shaheer Aboobaker
Position: Managing Partner, Toronto Retina Institute

Date: 28-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche		X		
Bayer	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Keyvan Koushan
Position: Partner
Date: 31-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer	X			
Novartis	X			
Allergan	X			
Apellis	X			
Alcon	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH Reimbursement Review
Drug Program Input on Implementation Issues

Section 1: General Information

1.1 Drug Product Information:	
Drug name (generic): TBC (aflibercept)	**Sponsor:** Bayer Inc.
Indication: For the treatment of diabetic macular edema (DME)	
Reimbursement Request: As per indication	

1.2 Lead Jurisdiction
Jurisdiction: **NB**

Section 2: Jurisdictional Implementation Issues

Table 1: Jurisdictional Context

2.1 RELEVANT COMPARATORS Check (type "X") whether you have identified potential or current **issues** and provide brief details	
☒	**a) Issues with the choice of comparator in the submitted trial(s)** • One phase 3, multi-centre, randomised, double-masked, active-controlled study (PHOTON). • PHOTON compared aflibercept high dose (8mg) to aflibercept (Eylea) 2mg for efficacy, safety, and tolerability and to determine if aflibercept 8 mg administered in two extended dosing regimens was non-inferior to Eylea 2 mg. • There were no trials comparing aflibercept 8mg with other anti-VEGF drugs (Beovu and Vabysmo) that can be administered at the same extended dosing interval.
☐	**b) Other implementation issues regarding relevant comparators (e.g., access/funding, covered population)** Example text: CAR-T could be considered a comparator in this population. However, its access is restricted to patients who have experienced three prior lines of therapy.

Table 2: Policy Considerations for Reimbursing the Drug

2.2 CONSIDERATIONS FOR INITIATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☒	**a) Disease diagnosis, scoring or staging for eligibility** • Most provinces have retinal programs and therefore no published criteria or criteria is not adjudicated against. • Some provinces have criteria that are in line with the inclusion criteria for PHOTON. Clinical trial inclusion criteria: • DMO with central involvement and CRT ≥300 µm (or ≥320 on Spectralis) as determined by the reading centre at the screening visit • BCVA ETDRS letter score of 78-24 (20/32 to 20/320 Snellen equivalent) in the study eye, with decreased vision attributed to DMO *Question for clinical experts:*

	Are the inclusion criteria reflective of current practice and appropriate as initiation criteria for DME .
☐	**b) Other patient characteristics for eligibility (e.g., age restrictions, comorbidities)** Example: Should patients having experienced a drug of the same class be eligible for the drug under review?
☐	**c) Prior therapies required for eligibility** Example: Should patients having experienced a drug of the same class be eligible for the drug under review?
☐	**d) Eligibility to re-treatment** Example: Can the drug be given again to patients who relapsed while off therapy? If so, what would be the appropriate timing of re-treatment?
☐	**e) Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility** Example: Would patients with CNS metastases equally benefit from this oncology drug and would they be considered eligible?
☒	**f) Consistency with initiation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** • Lucentis recommendation for Lucentis is from 2012 and included initiation criteria however, likely outdated as it includes a requirement for A1C. **Lucentis recommendation:** The Canadian Drug Expert Committee (CDEC) recommends that ranibizumab be listed, for patients meeting all of the following criteria: – clinically significant diabetic macular edema for whom laser photocoagulation is also indicated, and – a hemoglobin A1c of less than 11%, • Eylea 2 mg recommendation is from 2014 and was to list in a similar manner as Lucentis • Beovu and Vabysmo recommendations were to list in a similar manner to other anti-VEGF drugs. • A number of jurisdictions have since removed the requirement for A1C as part of initiation criteria. *Question for CADTH/clinical expert:* *Are the 2012 criteria for Lucentis in DME appropriate to be applied to aflibercept 8mg? If not, can criteria be provided. E.g. are the inclusion criteria for PHOTON more appropriate?*
2.3 CONSIDERATIONS FOR CONTINUATION OR RENEWAL OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Challenges related to assessment and monitoring of therapeutic response** Example: Need for regular brain MRI scans to monitor response to drug. There is limited access in some provinces.
☐	**b) Consistency with renewal criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with renewal criteria for drug B.
2.4 CONSIDERATIONS FOR DISCONTINUATION OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Definition of loss of response, absence of clinical benefit, or disease progression** Example: Need definition of refractory disease (based on what parameters?)
☐	**b) Treatment interruptions** Example: If there is progression during a “drug holiday”, can treatment be resumed? According to what timeframe?
☐	**c) Definition of fixed-duration therapy** Example: Should therapy end after x number of doses or after two years, whichever comes first?

☒	**d) Consistency with discontinuation criteria associated with other drugs reviewed by CADTH in the same therapeutic space** • No discontinuation criteria has ever been provided by CADTH for anti-VEGF drugs for DME. • Discontinuation criteria exists for AMD in some jurisdictions with publicly facing criteria. *Question for CDEC/clinical expert:* *Should discontinuation criteria be included in the recommendation?*
2.5 CONSIDERATIONS FOR PRESCRIBING OF THERAPY Check any category where you have identified potential or current **issues** and provide brief details	
☒	**a) Dosing, schedule/frequency, dose intensity** • 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 Beovu is 6 mg every 6 weeks for the first 5 doses then every 12 weeks. – Recommended dose of Vabysmo is 6 mg every 4 weeks for the first 4 doses then every 8, 12 or 16 weeks. *Question for clinical experts:* *Does aflibercept 8 mg meet an unmet need given there are other products marketed with an extended dosing interval?*
☐	**b) Drug administration** Example: Intrathecal administration requires special training and facilities.
☐	**c) Concerns related to accessing clinical specialists and/or special settings** Example: There is limited access to specialists within some regions.
☐	**d) Concerns related to combination usage** Example: The combination includes an oral and an IV drug that would be reimbursed through different programs.
☐	**e) Consistency with prescribing criteria associated with other drugs reviewed by CADTH in the same therapeutic space** Example: Consider alignment with prescribing criteria for drug B.

Table 3: Special Implementation Issues

2.6 GENERALIZABILITY Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Populations of interest matching the indication but with insufficient data** Example: Patients with ECOG performance status >1 were excluded from the trial. Can they be considered eligible?
☐	**b) Populations outside the indication or reimbursement request but of interest to jurisdictions** Example: Can this RA drug also be given to patients with giant cell arteritis?
☐	**c) Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review** Example: Potential need to allow switching patients currently receiving a comparator, if the drug under review is recommended and deemed superior.
2.7 FUNDING ALGORITHM (ONCOLOGY ONLY) Check any aspect that may require the development of a provisional funding algorithm by CADTH	
☐	Drug may change place in therapy of comparator drugs
☐	Drug may change place in therapy of drugs reimbursed in previous lines
☐	Drug may change place in therapy of drugs reimbursed in subsequent lines
☐	Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products
☐	Other aspects:

2.8 CARE PROVISION ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
☐	**a) Drug preparation, storage, administration or dispensing** Example: Drug needs to be initiated in the hospital setting while maintenance therapy would be provided in the community setting.
☐	**b) Management of adverse effects** Example: Tumour lysis syndrome needs to be monitored and managed in the hospital.
☐	**c) Additional supportive medication or other health interventions** Example: Immunosuppressive drug requires co-administration of prophylactic antimicrobials.
☐	**d) Companion diagnostics (e.g., access issues, timing of testing)** Example: Need advice on optimal timing of biomarker testing (e.g., at time of diagnosis, as part of eligibility assessment prior to initiation).
☐	**e) Other care provision issues** Example: To manage toxicity, can one drug of the pair be stopped and the other continued until loss of clinical benefit?
2.9 SYSTEM AND ECONOMIC ISSUES Check any category where you have identified potential or current **issues** and provide brief details	
☒	**a) Concerns regarding the anticipated budget impact and sustainability** • Aflibercept 8mg would have significant budget impact on public drug plans. BIA for New Brunswick was combined with other jurisdictions and does reflect current utilization. • Biosimilars have already been marketed for Lucentis • Biosimilars are anticipated for Eylea 2mg next year. • There are significant concerns regarding brand manufacturers marketing an improved version of an existing originator drug (i.e. evergreening) to maintain market share and extend patent. • There has been a significant increase in drug utilization in NB for Eylea 2 mg due to prescriber switching from Lucentis to avoid the recently implemented Lucentis biosimilar switch initiative. *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.*
☐	**b) Additional costs to be considered (other than related to care provision as detailed above)** Example: This therapy requires facilities that are not available in all provinces. Drug plans may need to cover travel expenses for eligible patients.
☐	**c) Involvement of additional payers** Example: The implantable device component of this therapy will need to be funded by medical services departments within jurisdictional health care systems.
☒	**d) Presence of confidential negotiated prices for comparators** • Confidential pricing agreements exist for most anti-VEGF drugs. • Based on current list price, aflibercept 8mg is not a cost-effective treatment option.
☒	**e) Special programs or initiatives for the introduction and management of the drug(s) under review** • Retinal programs/provincials eye centers exist in a number of provinces. • Avastin first policies in place in a number of provinces.
☐	**f) Other system or economic issues** Example: High upfront cost of this gene therapy may require special payment arrangements.