## CADTH REIMBURSEMENT REVIEW

# Patient and Clinician Group Input

## AFLIBERCEPT (Eylea HD)

## (Bayer Inc.)

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

**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 CADTH 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.

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# Stakeholder Input

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# Patient Input

## Patient Input 1

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:

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)

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.

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.

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

No

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

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 202

# Patient Input 2

Name of Drug: aflibercept (8mg)

Indication: Macular degeneration, age-related

Name of Patient Group: Fighting Blindness Canada, The Canadian Council of the Blind, CNIB, Vision Loss Rehabilitation Canada, International Federation on Ageing

Author of Submission: Dr. Larissa Moniz (FBC), Jim Prowse (CCB), Thomas Simpson (CNIB), Jennifer Urosevic (VLRC), Jane Barratt (IFA)

## 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.

Our community is diverse and thriving. FBC represents thousands of individuals and families affected by vision loss, volunteers, and scientists and clinicians seeking treatments and cures for blinding eye diseases.

**The Canadian Council of the Blind** (CCB) is a membership-based not-for-profit organization that brings together Canadians who are blind, deaf-blind or living with vision loss through chapters within their own local communities to share common interests and social activities.

CCB works to improve the quality of life for persons with vision loss through awareness, peer mentoring, socializing, sports, advocacy, health promotion and illness prevention.

Members participate as volunteers in the peer support, sports and recreation, book clubs, awareness, and educational activities of the CCB. Members manage the affairs of their own local chapters consistent with the National Canadian Council of the Blind and may be elected to executive functions locally, provincially and/or nationally. They serve on various committees at these levels as well as participating in many other community groups.

CCB chapter members may involve themselves at their own comfort level and may choose to learn new skills or sports, become involved in accessibility awareness, and educational activities or simply enjoy the company of others.

Membership provides inclusion, purpose, fellowship and social interaction with peers who understand and support each person’s unique strengths and abilities.

The CCB was founded in 1944 by blind Canadian war veterans and schools of the blind. The national office is located in Ottawa with over 80 chapters across Canada. The CCB is the largest membership-based organization for the blind in Canada and is known as the Voice of the Blind™.

The CCB's offers programs to assist people living with vision loss, increase accessibility in all areas of life and bring awareness of vision issues to the public and government. 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.

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

### Information Gathering

Information that forms the basis of this document was collected through an online survey made available to Canadians living with age-related macular degeneration (wet or dry AMD) during the first months of 2020. Shared across networks associated with FBC and CCB, the survey is part of a larger research project titled VIEW AMD (Valuation and Interpretation of Experiences with AMD) that received ethics approval from Advarra, the largest independent provider of institutional review board (IRB) services.

Our goal with the survey was to learn more about lived experiences of AMD, particularly perceptions of the disease, its treatments, and the specific burdens associated with living with both wet and dry AMD. We did not aim to learn more about aflibercept in comparison with other drugs, or to evaluate the effectiveness or safety of the drug in question (that is the precise role of RCTs).

Instead, we hope the following data and analysis provide insights into the lived experiences of Canadians with AMD, individuals who must navigate the often-daily barriers and burdens that accompany the disease. Our belief is that these perspectives are crucial, and that

they should be used to inform and guide decision-making related to any new treatment under consideration with the potential to address the physical, psychological, and socioeconomic burdens associated with the disease. We did ask 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, received aflibercept (2mg) and not the drug under review aflibercept (8mg).

*Overview of Respondents*

**A total of 337 Canadians responded to the survey.** Out of these, most were between either 61 and 80 (36.6%) or 41 and 60 (35%) years of age, with a roughly equal split between male and female; most were retired (55.3%) followed by those working full-time (21.1%). A majority of participants reside in urban regions (89%) and were from Ontario (44.8%), British Columbia (20.2%), and Alberta (10.4%), followed by smaller groups within Canada's other provinces and territories.

In terms of disease status, a significant number of patients indicated having wet AMD (47.1%), with the remainder indicating dry AMD(37.7%); Others respondents selected either wet in one eye, dry in the other (12.8%) or that they are not sure of the type (2.4%).

**Table 1. Baseline characteristics of respondents (n = 337)**

| **Characteristic** | **n (%)** |
|---|---|
| **Age (n = 320)** | |
| Mean age (SD) | 63.5 (16.5) |
| 18 - 40 years | 34 (10.6) |
| 41 - 60 years | 112 (35.0) |
| 61 - 80 years | 117 (36.6) |
| Over 80 years | 57 (17.8) |
| **Biological Sex (n = 322)** | |
| Female | 168 (52.2) |
| Male | 153 (47.5) |
| Intersex | 1 (0.3) |
| **Province (n = 337)** | |
| Ontario | 151 (44.8) |
| British Columbia | 68 (20.2) |

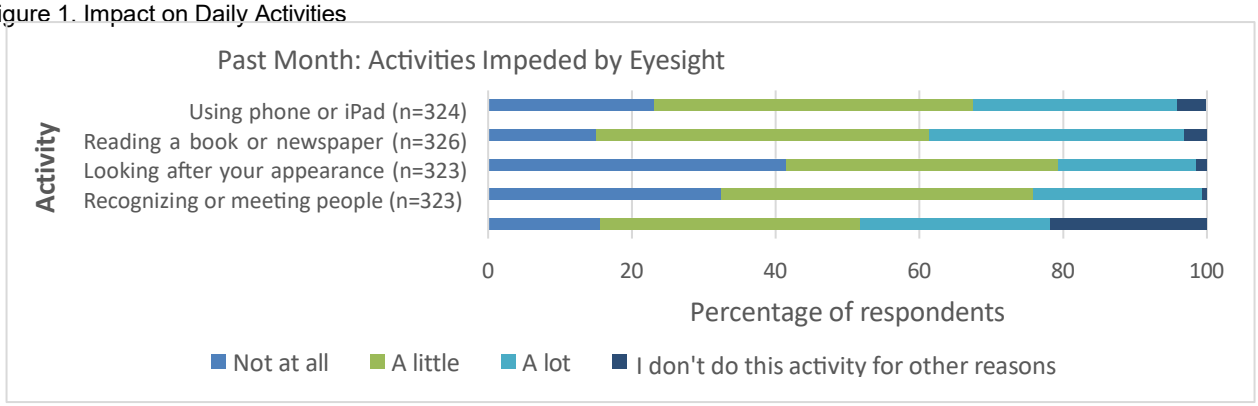
| | |
|---|---|
| Alberta | 35 (10.4) |
| Quebec | 25 (7.4) |
| Manitoba | 13 (3.9) |
| Nova Scotia | 12 (3.6) |
| Newfoundland | 11 (3.3) |
| New Brunswick | 7 (2.1) |
| Northwest Territories | 6 (1.8) |
| Prince Edward Island | 4 (1.2) |
| Saskatchewan | 4 (1.2) |
| Nunavut | 1 (0.3) |
| | |
| **Location (n = 337)** | |
| Urban | 300 (89.0) |
| Rural | 37(11.0) |
| | |
| **Type of AMD (n = 337)** | |
| Wet AMD in both eyes | 111 (32.9) |
| Dry AMD in both eyes | 60 (17.8) |
| Dry AMD in one eye | 67 (19.9) |
| Wet AMD in one eye | 48 (14.2) |
| Wet AMD in one eye and dry AMD in the other eye | 43 (12.8) |
| Doesn’t know AMD type | 8 (2.4) |
| | |
| **Other household members (n = 337)** | |

| | |
|---|---|
| Partner/spouse | 212 (62.9) |
| My child(ren) | 76 (22.6) |
| No one | 56 (16.6) |
| Family member(s) other than partner and child | 33 (9.8) |
| I live in a retirement home | 23 (6.8) |
| Roommate/friend | 12 (3.6) |
| I live in a nursing home/long-term care facility | 2 (0.6) |
| | |
| **Employment Status (n = 322)** | |
| Retired | 178 (55.3) |
| Employed, working full-time | 68 (21.1) |
| Employed, working part-time | 40 (12.4) |
| Homemaker | 18 (5.6) |
| Not employed, looking for work | 9 (2.8) |
| Unemployed due to illness or disability | 6 (1.9) |
| Taking care of a family member | 2 (0.6) |
| Other: *In training for new career* | 1 (7.7) |

Disease Experience

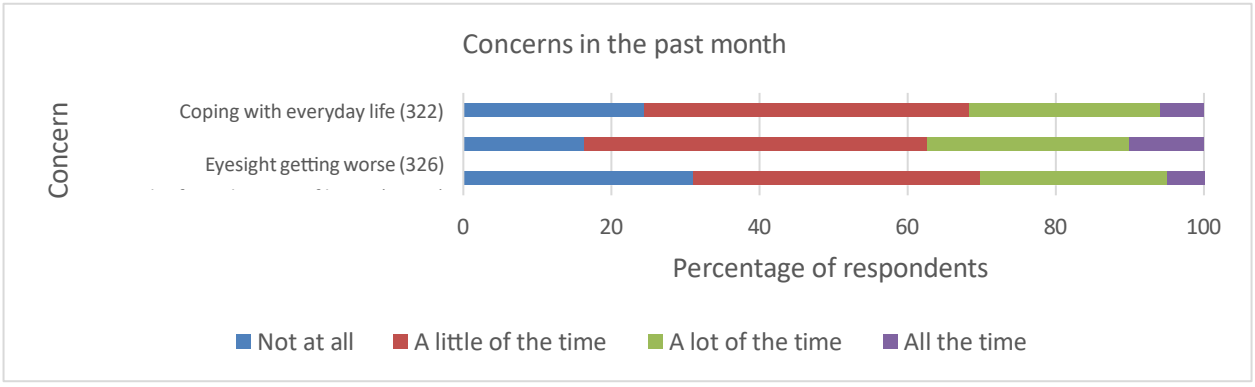
Perhaps more than anything else, respondents made it clear that the disease has a significant impact on their daily lives, manifesting as physical, psychological, and social impacts. The majority (60-80%) reported that sight loss resulting from AMD affects their daily activities (Figure 1) which includes personal care and hygiene, interacting with phones and tablets and reading books and newspapers.

Figure 1. Impact on Daily Activities




Beyond these largely physical impacts, it was also made clear that AMD affects patients psychologically in a profound way. For instance, approximately one-third of respondents sthink about their disease and its impacts either “all the time” or “a lot of the time,” implying that AMD carries a significant psychological burden (Figure 2).

Figure 2. Concerns Related to AMD



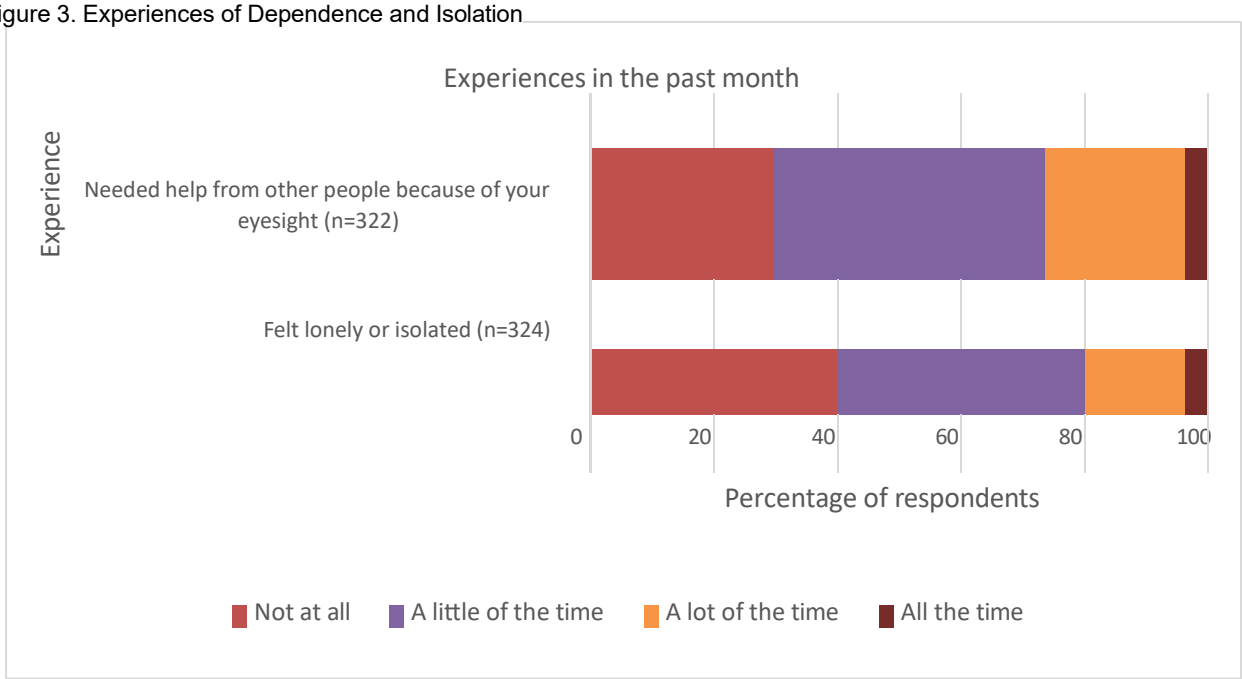

This psychological toll or burden was supported in relation to challenges as well. When asked to select from a list of challenges associated with sight loss and AMD, the majority indicated that they “worry that my condition might worsen in the future” (77%) (Table 2). AMD appears to weigh heavily on patients in terms of frequent thinking, then, but also in a future-oriented manner when it comes to the deterioration of vision over time. Other challenges included but are not limited to “not being able to do the daily activities I used to” (38.4%), “the long wait time for appointments” (31.2%), and more.

Table 2. Challenges with AMD (n = 330)

| Challenges | n (%) |
|---|---|
| Worry that my condition might worsen in the future (n=331) | 255 (77.0) |
| Not being able to do the daily activities I used to (n=331) | 127 (38.4) |
| The long wait times for appointments | 103 (31.2) |
| Explaining my condition to family and friends | 103 (31.2) |
| Lack of social support | 97 (29.4) |
| Finding answers to my questions about my condition | 73 (22.1) |
| Socializing | 68 (20.6) |
| Other* | 34 (10.3) |

The disease carries social implications as well. When asked about needing assistance and about feelings of isolation, respondents made it clear that they often rely on others because of their sight, and approximately 60% reported feeling lonely or isolated in the last month (Figure 3).

Figure 3. Experiences of Dependence and Isolation




In fact, the need for assistance emerged as a recurring theme for respondents. For instance, in a separate question related to injection appointments, over 85% of those who receive injections indicated requiring help when they go to their appointments. It is safe to assume that the burdens associated with these appointments increase when they are more frequent. This note is supported by new research demonstrating the significant physical and psychological burdens associated with anti-VEGF injections.[1]

It is clear that AMD has a strong impact on the lives of those who are affected by it. Whether it be in relation to reading or worrying or relying on others, the disease tends to deeply 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 AMD as a significant or considerable burden on the daily lives of patients.

## Experiences With Currently Available Treatments

Three-quarters (3 out of 4 respondents (75.4% indicated that they currently receive injections as a treatment for their AMD. Of those receiving injections the most common brand was Avastin (29.4%), followed by Lucentis (24.6%), aflibercept (20.2%), and Ozurdex (13.5%). The remainder of patients did not know the brand of their injection, were receiving multiple, or received the injection as part of a blind study. As noted above, due to the timeline of the study, it is assumed that participants who indicated receiving aflibercept, received aflibercept (2mg) and not aflibercept (8mg).

*Satisfaction and Adherence*

Almost one-half (46%) are “satisfied” with their injections and that “they helped me avoid losing more eyesight” (72.7%) (Table 3, Table 4).

Table 3. Level of satisfaction with injections (n = 252)

| | **n (%)** |
|---|---|
| Very dissatisfied | 1 (0.4) |
| Dissatisfied | 8 (3.2) |
| Neither satisfied nor dissatisfied | 46 (18.3) |
| Satisfied | 116 (46.0) |
| Very satisfied | 81 (32.1) |

**Table 4. How the injections have helped (n = 253)**

| | **n (%)** |
|---|---|
| They helped me avoid losing more eyesight | 184 (72.7) |
| They improved my eyesight | 112 (44.3) |
| Dried up fluid/blood in my eye(s) (n=252) | 104 (41.3) |
| They have had no effect but I receive injections because my doctor recommends them | 43 (17.0) |
| I don't know | 7 (2.8) |
| Other* | 8 (3.2) |

At the same time, it is worth noting that almost 20% of respondents who are currently receiving injections think that they have no beneficial effect or are unsure if there is an effect.

[1] G Reitan, IBK Haugen, K Andersen, et al. Through the Eyes of Patients: Understanding Treatment Burden of Intravitreal Anti-VEGF Injections for nAMD Patients in Norway, *Clinical Ophthalmology*, 2023. 17:1465-1474, DOI: 10.2147/OPTH.S409103

Although most respondents reported not missing an injection appointment in the last year (67.9%), a sizeable percentage indicated missing at least one appointment (32.1%) (Table 5). The most common reason for missing an appointment was being "unable to find someone to take me to the appointment" (39.5%), recalling the earlier suggestion of dependence being a key aspect of the experience of AMD. This response was followed closely by being "unable to travel to appointment" (34.6%) and "could not afford attending the appointment" (30.9%).

It is clear in these responses that some of the difficulty in attending injection appointments is found not in the experience of the injection itself, but in the logistics of travel and payment. It is fair to assume that these difficulties are exacerbated for those living in Canada's rural and remote communities, where access to specialized care is often limited, and where the average distance to the nearest specialist is significantly more than in more urban locations. A treatment that requires fewer injections could help minimize some of these challenges.

Table 5. Reason for cancellation or delay (n = 81)

| **Reason for cancellation or delay** | **n (%)** |
|---|---|
| Unable to find someone to take me to the appointment | 32 (39.5) |
| Unable to travel to appointment | 28 (34.6) |
| Could not afford attending the appointment | 25 (30.9) |
| Too busy to attend appointment | 20 (24.7) |
| Did not know how important the injection was to my sight | 20 (24.7) |
| Scared to receive the injection | 11 (13.6) |
| Did not find previous injections helpful | 10 (12.3) |
| I forgot about the appointment | 4 (4.9) |
| I was not feeling well | 7 (8.6) |
| Other* | 11 (13.6) |

*Travel and Time Commitment*

Almost half of the respondents indicated facing a travel time of 31 - 60 minutes to get to their injection appointment, followed by under 30 minutes (29.4%) and between 1 and 2 hours (15.5%). While at the appointment, most respondents reported waiting for more than 1 hour but less than 2 (60.8%), followed by less than 1 hour (17.6%) and, at the other end of the spectrum, more than 2 hours but less than 4 (16%)—groups that are very close in size.

The experience of ease or difficulty related to travel was varied among respondents, with most selecting that travel is generally “easy” (39.3%) followed by “neither easy nor difficult” (31.3%) (Table 7). A smaller group selected “difficult” (7.1%) and, when asked what makes the travel challenging, reported that distance (50%) and vehicle condition (30%) are notable factors (Table 7).

Table 6. Experience of travel to injection appointments? (n=252)

| **Ease of travel** | **n (%)** |
|---|---|
| Very difficult | 2 (0.8) |
| Difficult | 18 (7.1) |
| Neither easy nor difficult | 79 (31.3) |
| Easy | 99 (39.3) |
| Very easy | 54 (21.4) |

**Table 7. Reasons for difficult travel to your injection appointments (n=20)**

| **Reason** | **n (%)** |
|---|---|
| It is far from home | 10 (50.0) |
| My vehicle is in poor condition | 6 (30.0) |
| Poor road conditions | 5 (25.0) |
| It is expensive to travel | 5 (25.0) |
| Other* | 2 (10.0) |

Despite a smaller number of patients finding travel difficult, it is worth noting that wait times and travel still ranked high as difficult aspects of the injection appointment overall. When asked what is the most difficult part of the appointment, 30.5% of patients selected “long waiting time at the appointment,” 28.9% selected “cost of travel to/from the appointment,” and 27.7% selected “finding someone to drive me to/from the appointment” (Table 8). For these patients, the experiences of travel and waiting exist as significant hurdles or challenges. More research and analysis are needed to determine if there is an overlap between these experiences and non-adherence.

Table 8. Most difficult part of eye injection appointments (n = 249)

| Reason | n (%) |
|---|---|
| Anxiety or fear about the injection | 95 (38.2) |
| Long waiting time at the appointment | 76 (30.5) |
| Cost of travel to/from the appointment | 72 (28.9) |
| Finding someone to drive me to/from the appointment | 69 (27.7) |
| Finding someone to help me with my daily tasks after the injection | 56 (22.5) |
| I don't find any part difficult | 52 (20.9) |
| Scratchiness or pain in my eye after the appointment | 46 (18.5) |
| Taking time off work to attend | 31 (12.4) |
| Other** | 8 (3.2) |

Importantly—and perhaps unsurprisingly—respondents in rural parts of Canada were significantly more likely to travel more than 1 hour to attend appointments (30.3% for rural patients compared to 11% for those in urban regions). They were also more likely to describe their travel experience as “difficult” (18.2% compared to 5.5%). This underscores the issue mentioned above that, despite what the overall experience may be, those patients facing more significant barriers to care need to be valued and considered in the development and approval of new drugs. In this case, treatments that lessen the burden on travel for rural and remote patients would likely be considered desirable.

*Emotional and Physical Effects*

Besides difficulty in relation to travel, cost, and waiting, the largest group of patients underscored “anxiety or fear about the injection” (38.2%) as the most difficult part of the appointment (see the above table). 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 AMD 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.

Results in the above table also make it clear that the physical effects of injections are not to be ignored—for instance, 18.5% of patients selected “scratchiness or pain in my eye after the appointment” as a difficulty. At the same time, when asked how painful the injections are during the appointment, although almost a quarter of patients selected “not painful at all” (24.3%), the largest group selected “slightly painful” (54.6%) and a sizeable number selected “painful” (19.5%) (Table 9). And for some, the emphasis on pain increases into the evening, with 56.9 % of patients reporting their experience of pain as “slightly painful” into the evening, and 19% reporting a “painful” experience (Table 10). In total, approximately 4 out of 5 patients experience at least some pain lingering into the evening after their injection appointments.

Table 9. Painfulness of the injection (n=251)

| Reason | n (%) |
|---|---|
| Not painful at all | 61 (24.3) |
| Slightly painful | 137 (54.6) |
| Painful | 49 (19.5) |
| Extremely painful | 4 (1.6) |

**Table 10. Experience of pain into the evening after the injection (n=248)**

| Reason | n (%) |
|---|---|
| Not painful at all | 51 (20.6) |
| Slightly painful | 141 (56.9) |
| Painful | 47 (19.0) |
| Extremely painful | 9 (3.6) |

Visual complications are also a factor for many patients, with many experiencing blurry vision for 1 - 3 hours after the injection (48.2%), followed by 4 - 6 hours (25.9%) (Table 11). For respondents, these complications made certain activities impossible post- injection—significantly, all respondents indicated that they were unable to conduct at least one regular activity after their injection, with the largest group selecting “watch TV” (49.1%), followed by “read” (42.1%) and “drive” (30.4%) (Table 12).

Table 11. Duration of blurry vision post-injection (n=247)

| Frequency | n (%) |
|---|---|
| Less than 1 hour | 26 (10.5) |
| 1-3 hours | 119 (48.2) |
| 4-6 hours | 64 (25.9) |
| For at least 24 hours | 16 (6.5) |
| Until I go to sleep that night | 22 (8.9) |

**Table 12. Activities that are not possible post-injection (n=214)**

| Activity | n (%) |
|---|---|
| Watch TV | 105 (49.1) |
| Read | 90 (42.1) |
| Drive | 65 (30.4) |
| Prepare meals | 60 (28.0) |
| Provide care to family members* | 32 (15.0) |
| Work* | 26 (12.2) |
| None of the above activities | 0 |

Respondents also made it clear that, due to these complications, they require assistance more frequently after their injections. When asked what kind of assistance they receive in general, the largest group indicated that they require help “after the injections with everyday tasks” (55.7%) (Table 13). This once again emphasizes the theme of a lack of independence experienced by those with AMD, who in many cases not only rely on friends and loved ones for travel to and from injection appointments, but for help with tasks afterwards as well.

Table 13. Type of help provided post-injection

| | n (%) |
|---|---|
| Help me after the injections with everyday tasks | 118 (55.7) |
| Wait with me at the appointment | 116 (54.7) |
| Travel with me or drive me to/from the appointment | 114 (53.4) |
| Take care of things at home while I am away | 69 (32.5) |
| Physical support at my appointment | 51 (24.1) |
| Other* | 3 (1.4) |

These responses emphasize the emotional and physical impacts of AMD, making it clear that the disease exacts a physical and psychological toll that exists alongside the logistical challenges associated with travel and time.

### Improved Outcomes

Our survey did not ask patients for their views on improving their experiences and outcomes. In previous patient engagements, however, we did learn that most patients would prefer a treatment or medication type that can be taken less frequently.

In a previous survey, when asked whether a treatment that can be taken less often would be preferred, the majority of patients (64%) with wet AMD indicated “yes”. When asked whether they think the public health system should pay for better medication and treatments for AMD, 61% of patients with wet AMD indicated “yes.

### Experience With Drug Under Review

As discussed under Section 4, while approximately 15% of participants indicated receiving aflibercept as a treatment, it is assumed that this was aflibercept (2mg) and not aflibercept (8mg) 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)).

### Companion Diagnostic Test

Not applicable

### Anything Else?

AMD is a chronic disease that creates a range of challenges and burdens for patients. For many of the 337 Canadians that responded to our survey, their AMD leads to visual complications that render certain daily activities—such as reading or driving— either problematic or impossible. AMD is therefore physically and visually burdensome, and its corresponding emotional and psychological burdens are acute for patients as well. For example, many patients indicated that they think about their disease frequently, especially its impact on their future, and that they experience fear or anxiety in relation to their injection regimes. As a result of patient input regarding the experience of the disease and its treatment, it is clear that a treatment with a less demanding injection regime would help ease some of the burden associated with AMD.

Thanks to modern research, anti-VEGF injections are now the frontline treatment for patients with wet-AMD, replacing forms of surgery that once had significant drawbacks. While the various anti-VEGF drugs on the market have shown high levels of effectiveness in slowing or halting loss of vision, it is also the case that the need for regular—often monthly—injections directly into the eye have created challenges for many patients. This is borne out in our survey results, with groups of respondents emphasizing the painfulness of the injection, both during and after the procedure, and their difficulties managing travel to and from injection appointments. The issue of travel is especially pronounced for those living in rural and remote parts of Canada, who often travel significant distances to receive their injections. The challenges associated with AMD also lead to many patients relying on loved ones to assist them; they often receive aid in travelling to and from appointments, and in managing the tasks that are made difficult by AMD and by the short-term visual complications that result from injections. As a result, there is a common thread running through the responses that the disease leads to a certain lack of independence. Many patients would prefer a treatment that can be taken less frequently, are supportive of public funding being used in the advancement of such a treatment and are open to participating in clinical trials.

More research is required to better understand the reasons for why certain patients with AMD miss their appointments or stop them altogether. That said, contemporary research has shown that both non-adherence and non-persistence are quite high with this group: for instance, a recent study showed that close to 50% of patients stop anti-VEGF treatments after 24 months.[2] It is entirely possible that the impacts shown in this report—issues with travel and other logistical challenges, as well as physical and psychological effects—could play a significant role in this drop off. With this in mind, treatments that lessen the burdens on this group could play an important role in countering the trend of non-compliance and under treatment.

This is a snapshot of the experiences of patients with AMD 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;

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[2] 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

and the psychological and emotional tolls of the disease. As organizations that represent patients with AMD 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 AMD and their value in the review process of new treatments.

We look forward to continuing to work with CADTH to support Canadians living with AMD, and to advance our collective understanding of how the disease and its treatments impact their lives.

## 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.

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.

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.

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 | | | | 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 |
|---|---|---|---|---|
| **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

# Clinician Input

## Clinician Group Input 1

CADTH Project Number: SR0812-000

Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL

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

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 nAMD 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 nAMD). 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. For example, scarring in nAMD may cause irreversible damage to vision. 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 nAMD 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 nAMD 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 cautiously for patients with nAMD to prevent disease recurrence which can lead to irreversible vision loss.

### 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 nAMD 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.

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.

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

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. 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**

| | **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 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.

# Clinician Group Input 2

CADTH Project Number: SR0812-000

Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL

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

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 nAMD 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.

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 nAMD, 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.

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.

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

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**

| | **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 | | | |
| 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**

| | **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 | | | |
| 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**

| | **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.

# Clinician Group Input 3

CADTH Project Number: SR0812-000

Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL

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

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

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, allowing for socialization and holding employment

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 PULSAR trial showing 88% 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 a 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.

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.

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

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**

| | **Check appropriate dollar range*** | | | |
|---|---|---|---|---|
| **Company** | **$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.

# Clinician Group Input 4

CADTH Project Number: SR0812-000

Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL

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

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 nAMD 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.

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.

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.

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**

| | **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 | | | |

* 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.

# Clinician Group Input 5

CADTH Project Number: SR0812-000

Generic Drug Name (Brand Name): Aflibercept 8mg

Indication: neovascular AMD

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, Conference presentations, systematic reviews and meta-analyses.

3. Current Treatments and Treatment Goals

Age related macular degeneration (AMD) is the leading causes of blindness in Canada, affecting nearly 2 million Canadians at present. Neovascular AMD (nAMD) accounts for the vast majority of severe vision loss for patients with AMD .

The current gold standard treatment for neovascular AMD in Canada is serial intravitreal anti-VEGF therapy. This has been established by robust meta-analysis research (Solomon et al, Cochrane Database Syst Rev. 2019, Mar 4;3(3)) and by guidelines from major global ophthalmology societies (such as the American Academy of Ophthalmology and the European Retina Society). These agents have revolutionized the treatment for nAMD globally and within Canada. Although very effective at improving vision and maintaining vision in clinical trials, real world evidence from Canada suggests that visual outcomes are suboptimal due to the intense treatment burden for the current agents. The Luminous study, which included a Canadian subset of patients with nAMD undergoing anti-VEGF treatment, demonstrated that real-world treatment was associated with sub-optimal treatment intensity and subsequent vision loss over time when compared to outcomes from randomized clinical trials. The burden of frequent treatment with current anti-VEGF agents has led to an efficacy gap whereby clinical trial results have been very difficult to replicate in real world practice. In addition, recent challenges with the pandemic and limitations to health care delivery has further compromised the ability to provide regular and timely treatment for patients who require very regular and intense treatment.

The current treatments do modify the disease process by minimizing growth and exudation of the choroidal neovascular membrane in nAMD. This manifests as a fluid and blood free retina and less or no fibrosis compared to natural history and older treatment modalities such as thermal laser or Photodynamic Therapy (PDT) . Nevertheless, fibrosis and atrophy remain the major causes for long-term vision loss in patients with nAMD.

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.

1) Treatment burden: Data from the IRIS registry in the US suggests that on average patients are being treated every 7 to 8 weeks after an intensive monthly loading treatment cycle for nAMD to maintain their vision. This represents a high burden for the health care system, physician, patients, and family members who must take time off work to attend clinic appointments and the frequency of these appointments does not decrease with time. Those patients (approximately 50%) who need more frequent treatment than every 8 weeks have a very high treatment burden. Recently, Faricimab was approved by Health Canada for nAMD management. This agent has demonstrated a strong durability signal and Phase III studies have demonstrated that approximately half the patients could extend treatment time to every four months. However, nAMD in a multi-factorial disease with a number of ocular, systemic and genetic risk factors at play. To optimize outcomes for Canadian patients, it is imperative that other durable treatment options with different MOA that demonstrated efficacy and safety are made available to help individualize care and optimize outcomes. Aflibercept 8mg was studied in the Phase 3 PULSAR study. In this study, Aflibercept 8mg demonstrated similar vision gains with fewer injections compared to a robust gold standard arm of fixed dose treatment with Aflibercept 2mg. There was a strong durability signal. 83% of 8mg nAMD patients in

PULSAR were maintained with injections every 12-16 weeks through the 1st year. In the second year, patients were allowed to be extended beyond 4 months, which is a paradigm shift in extension intervals and durability in a phase 3 program with intra-vitreal injection treatment in nAMD. The evidence from PULSAR demonstrated that 47% of nAMD patients were assigned to 20-24 week intervals.

2) Improved long term outcomes: Results from the CATT trial demonstrated that at 5 years, about 50% of patients have visual acuity worse than 20/40. Thus, although patients gained vision on average in the CATT trial in the first 2 years whilst being treated by a strict protocol mandated regimen, in the long term follow up phase that is more reflective of the "real-world" scenario, patients actually lost vision at year 5 compared to baseline. The main reasons for this were the development of atrophy and fibrosis which can develop when disease activity is poorly controlled. Patients with ongoing exudation and fluid fluctuation due to poor disease control are more likely to develop fibrosis and atrophy. As such, agents that are effective at drying the retina for a longer period of time and reducing treatment burden can theoretically provide improved long-term visual outcomes. PULSAR trial demonstrated that despite a significant reduction in number of treatments, disease control was maintained. Of those assigned to >/= 16 week dosing regimen at baseline, 70% maintained >/= 16 week dosing intervals throughout the two year study period.

3) 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. There were no new safety concerns with Aflibercept 8mg in the nAMD phase 3 program. Importantly, no cases of retinal vasculitis were noted.

One of the most important unmet needs in nAMD treatment is durability and reduced treatment frequency. Reducing treatment burden and allowing a fluid-free retina for a longer duration should allow for maintenance of maximal vision gains over the lifetime of the patient. 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 nAMD 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 nAMD.

Although rare, each intravitreal injection caries the risk of potentially devastating complications such as endophthalmitis which can lead to permanent vision loss or even loss of the eye itself. An agent which has a more durable treatment effect will reduce the number of injections required by a patient and thus expose the patient to less risk from the injection procedure itself.

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. Aflibercept 8mg has a different mechanism of action than Faricimab. 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, 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 nAMD 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, Aflibercept 8mg in the PULSAR trial tested and provided robust evidence for a paradigm shift in how nAMD care can be managed. This trial demonstrated that early rapid extensions immediately after 3 monthly loading doses with 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 Aflibercept 8mg 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?

As with all agents used in nAMD, treatment naïve patients would be the most likely to respond as demonstrated in the pivotal phase III trials. Other possible candidates would include patients with persistent disease activity despite aggressive treatment with other agents, or suboptimal response to other agents.

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 hemorrhage 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 in vision 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.

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

No

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

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:** August 27, 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 | | |
| 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**

| | **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 | | |
| 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**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| Company | $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.

# Clinician Group Input 6

CADTH Project Number: SR0812-000

Generic Drug Name (Brand Name): aflibercept 8 mg/0.07 mL

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

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 nAMD 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 nAMD), 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.

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. **CADTH Clinician Group Input Template** CADTH Reimbursement Reviews March 2022 2

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 with nAMD are of older age and often 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 PULSAR Trial and thus is the only treatment with robust evidence supporting extended dosing intervals. Indeed, instead of every two months, 88% 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 BYOOVIZTM, 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 nAMD 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 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. 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<br>Company | | Check appropriate dollar range* | |
|---|---|---|---|
| \$0 to<br>\$5,000 | \$5,001 to<br>\$10,000 | \$10,001 to \$50,000 | In excess of \$50,000 |

| | |
|---|---|
| Bayer | X |
| Novartis | X |
| Bausch + Lomb | X |