CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

lecanemab (Leqembi)

(Eisai Canada)

Indication: Lecanemab is indicated as a disease-modifying treatment in adult patients with Alzheimer's disease. Treatment with lecanemab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease.

June 17, 2024

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.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions received.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Group Input

Name of Drug: Leqembi (lecanamab)

Indication: To slow the clinical decline associated with Alzheimer's disease (AD) progression in patients with early AD or mild cognitive impairment (MCI) due to AD

Name of Patient Group: Alzheimer Society of Canada

Author of Submission: Luca Pisterzi

1. About Your Patient Group

The Alzheimer Society of Canada is the leading nationwide health charity supporting people living with all forms of dementia, including Alzheimer's disease, as well as their caregivers and their families. We work to identify, develop and facilitate national priorities that enable our members to effectively alleviate the personal and social consequences of Alzheimer's disease and other dementias.

Active in communities across Canada, the Society offers information, programs and support services, fundraises to advance research, advocates for policy change and increases public awareness of Alzheimer's disease and other dementias.

We rely on individual and corporate donors, communities and health-care partners to help us deliver on our mission. Additionally, we do not receive donations from pharmaceutical companies.

The Research, Knowledge Translation and Exchange, Partnerships and Programs department at the Alzheimer Society of Canada contains staff with expertise from many different perspectives. Our staff bring with them extensive experience in dementia research, aging and health care, data analysis and evaluation, project management, care coordination, and knowledge translation and exchange practices.

We are proud of the co-design approach we take in creating materials, programs and throughout all research processes. This is done through our robust and active National Advisory Group consisting of over 70 members. The Advisory Group of People with Lived Experience of Dementia is the heart of the Alzheimer Society of Canada. Our members make a significant impact on our work, including dementia research, education and advocacy.

alzheimer.ca/en | alzheimer.ca/fr

2. Information Gathering

Online surveys were conducted between May 24th, 2024 and June 10th, 2024. Two different surveys were developed and conducted: one for patients and one for caregivers. Surveys were conducted in English and French. Patients and caregivers were asked questions about the impact of Alzheimer's disease or Mild Cognitive Impairment (MCI) on the lives of patients and the effect of current treatments as well as questions directed to people with Leqembi (lecanemab) experience.

Additionally, staff at the Alzheimer Society of Canada provided their professional expertise within this submission. This included providing relevant research to consider as well as experiences gathered through working with people living with dementia and their caregivers.

A multimedia strategy was launched between May and June that utilized the Alzheimer Society of Canada website, social media channels, mailing lists, provincial and local newsletters, researcher and clinical networks, and broader partner organizations. A targeted approach was taken in reaching out to all clinical/sites that participated in the Leqembi (lecanemab) trials (publicly available data) in Canada to share information about the survey with their patients and caregivers.

Overall, 153 people completed the surveys. A total of 42 people completed the patient survey. 36 English respondents who responded to the patient survey consented for their data to be used. 1 English respondent lived in Quebec and therefore was

referred to INESSS to submit a response. 2 French respondents were in Quebec, and therefore were referred to INESSS to submit a response.

A total of 111 people completed the caregiver survey. 101 English respondents who responded to the caregiver survey consented for their data to be used. 3 English respondents lived in Quebec and therefore were referred to INESSS to submit a response. 2 French respondents were in Quebec, and therefore were referred to INESSS to submit a response. All respondents except for one are from Canada (representing Alberta, British Columbia, New Brunswick, Nova Scotia, Ontario, Saskatchewan, Manitoba, Newfoundland and Labrador and Prince Edward Island). The one other respondent is from Australia.

Patients		Caregivers	
English	French	English	French
36	2	101	2

A total of 7 people completed the survey specific to Leqembi (lecanemab) treatment: 4 patients and 3 caregivers; 7 in English and 0 in French. The respondents are from Nova Scotia and Ontario.

Patients		Caregivers	
English	French	English	French
4	0	3	0

3. Disease Experience

From the survey, 13 of the patients in these surveys have MCI, 10 have early-stage Alzheimer's disease, 5 have middle-stage Alzheimer's disease, 0 have late-stage Alzheimer's disease and 6 do not know or did not answer. Memory loss was the most commonly reported symptom of Alzheimer's disease or MCI by patients (88% n=30), followed by anxiety (55% n=19), becoming withdrawn (50% n=17) and depression (50% n=17).

From the caregiver survey, 20 people they cared for had mild cognitive impairment, 25 people they cared for had early-stage Alzheimer's disease, 15 people they cared for had late-stage Alzheimer's disease and 11 do not know or did not answer.

For caregivers, memory loss was the most reported symptom observed in the person they are supporting (97% n=101), followed by anxiety (67% n=70), changes in behaviour (63% n=66) and disorientation/getting lost (62% n=65).

If the person with Alzheimer's disease or MCI progressed from MCI to Alzheimer's disease, this changed the health and social care services that patients and caregivers accessed. Patients reported there was a lack of services offered in their region or had difficulty finding them or reported receiving respite services or attending day programs. Caregivers reported an increase in the home care or respite services accessed, such as having assistance from personal support workers. Many reported not having enough support. Some caregivers also reported that the person they cared for had moved into long-term care.

Caregivers reported the following concerning changes to their caregiving role over time:

- The most common response (n=23) was that caregivers are unable to leave the person at home alone and are required to give up other aspects of their life to provide care.
- The next most common response (n=22) was that caregivers increased the amount of personal care they provide to the person. For example, activities of daily living (personal hygiene, grooming, bathing, eating, toileting or transferring). Caregivers also reported helping the person with instrumental activities of daily living (e.g., shopping (n=9), cooking (n=12), dressing (n=6), cleaning (n=4), transportation (n=10), managing finances (n=9) and medications (n=9).

- Some caregivers (n=3) also reported needing to quit their jobs or move to part-time work to provide care, giving up their social life (n=2), experiencing caregiver burnout (n=3), and providing care to others such as children (n=3).

General information about the disease experience

Alzheimer's disease is a chronic neurodegenerative disease that eventually affects all aspects of a person's life. Due to the progressive nature of most dementias, people with dementia who live at home will eventually need increasing levels of medical and social support (to the point where the person needs 24-hour care), which may ultimately present challenges to their family and friends who act as caregivers. Canadian statistics (CIHI, 2018b) have shown that for people living with dementia:

- 1 in 4 require a lot of help for activities of daily living (e.g., eating, dressing, personal hygiene)
- 1 in 4 experience behavioural changes (e.g., anger, delusions, getting lost, restlessness, hallucinations, paranoia)
- 1 in 4 have symptoms of depression
- 1 in 4 were admitted to hospital at least once in the last three months
- 1 in 5 have been to an emergency room in the last three months

According to Nimmons et al. (2023), dementia leads to multiple issues, including difficulty in communication and increased need for care and support. Additionally, their study suggests that discussions about advance care planning often happen late in the process, or not at all. It is suggested that this may be due to reluctance, fear or stigma. Maintaining the person's identity and social connections, as well as living well with dementia, may help health-care providers have advance care planning conversations with patients.

There are many different challenges that caregivers for people with dementia experience. Here are some examples from the Canadian Institute for Health Information (2018b):

- 26 mean hours a week of informal care are provided to seniors with dementia, compared to other seniors.
- Unpaid caregivers of seniors with dementia are more likely to experience distress (45%) than caregivers of other seniors (26%). Some drivers of distress among caregivers are higher cognitive impairment, mood and behavioural symptoms of people receiving care (e.g., moderate to severe cognitive impairment, depression, anger/confusion, delusions, wandering and responsive behaviours) that occurred at least once in the last 3 days.
- $1.4 billion was the estimated total out-of-pocket costs paid for by caregivers of people with dementia in Canada in 2016.
- Financial challenges for caregivers of people with dementia consist of but are not limited to: home modifications, professional health care or rehabilitation services, hiring people to help with daily activities, transportation, specialized aids and/or prescription or non-prescription drugs. Depending on stage of life, caregivers may have to leave work to care for the person with Alzheimer's disease or MCI. This impacts their financial stability and ability to participate fully in life.

The goal of treating Alzheimer's disease is to manage and alleviate the symptoms and increase quality of life/wellbeing for both the person living with dementia and caregivers. However, some symptoms of Alzheimer's disease may be more important to manage than others, if they put the person or others around them at harm. For example, the person with dementia demonstrating physical aggression or irritability may put caregivers at harm, which could lead to physical or emotional abuse. Additionally, if a person living with Alzheimer's disease frequently leaves secure areas, like the home, and becomes lost, this is both a risk to the person with dementia as well as others around them. Another term for this is called "wandering," and research suggests that this occurs in approximately 15 to 60% of people living with dementia (Cipriani, Lucetti, Nuti & Danti, 2014). Search and rescue missions can be costly for governments and emotionally distressing for family and friends.

4. Experiences With Currently Available Treatments

129 respondents provided information about the treatments that they or the person for whom they are caring has received since their diagnosis. 19 different drugs were discussed by respondents.

Treatments Received	n	Treatments Received	n
Aricept (donepezil)	68	Atorvaststatin	1
Exelon (rivastigmine)	6	Donanemab	1
Namenda (memantine)	10	Quetiapine	2
Razadyne or Reminyl (galantamine)	17	Lecanemab	1
Lisinopril	1	Souvenaid supplements	1
Risperidone	2	Seroquel	1
Trazadone	1	Fluoxetine	1
Estradiol	1	Mirtazapine	2
Citalopram	2	Sertraline	5
Melatonin	1	Prefer not to answer	3
I don't know	8		

Patient and caregiver comments about the benefits of currently available treatments were split between people who reported positive benefits and those who reported no improvements. Current treatments do not consistently meet the medical needs of all individuals.

For example, some medications were reported to slow memory loss, but the person with dementia still inevitably worsened/will worsen over time. Additionally, many people reported that they do not know if the treatments are helping due to the progressive nature of the disease.

The following are some positive experiences with the above treatments.

- Citalopram
    - helped somewhat with anxiety (1).
    - sleeps better and less depressed (1).
- Rivastigmine
    - helped with being able to do household chores (1).
    - stabilized symptoms for more than one year (1).
    - stabilized condition (1).
    - unknown if helping (1).
- Galantamine
    - helped with slowing the dementia and memory loss (4).
    - don't know if has helped with progression (1).
    - helped for a number of years, declined faster once removed from drug (1).
    - feels more relaxed (1).
    - better mood (1)

- Aricept
    - believed to have helped with memory and have not observed worsening of symptoms (10)
    - helped with delusions, paranoia, depression (1).
    - still able to attend to personal hygiene (1).
    - not sure if there are any changes (10).
    - was unable to stay on it long enough for positive results (1).
    - saw improvement when first started taking medication, but this has since dropped off (4).
    - no changes seen (4).
    - too early to tell (1).
- Donanemab
    - believe it improved symptoms while taking it (1).
- Sertraline
    - helped with anxiety (2).
- Souvenaid supplements
    - too soon to tell yet if it helps (1).

- Donepezil
    - some decline in symptoms after starting treatment (1).
    - appeared to help with memory and mood (3).
    - unknown if helping (1).
- Seraquil
    - helps with anxiety (1).
- Memantine
    - can still drive and take care of self (1).
    - slight improvement in restlessness (1).
    - helped at beginning (1).
- Lecanamab
    - seemed to slow progression (1).

The following are some negative experiences with the above treatments.

Some negative experiences described by patients with the above treatments included: diarrhea, strange dreams and depression.

Caregivers described some negative experiences they observed as the person with Alzheimer's disease or MCI received the treatments above. Some responses were, violent behaviour or aggression, needing the drugs in different forms, such as in crushed

form or a liquid form. Many caregivers expressed it was hard to know if negative experiences, such as increased confusion, were due to the disease progressing, or the medications the person were taking.

The majority of patients reported experiencing no side effects of treatments (42% n=12). The most common side effects experienced were dizziness (25% n=7) followed by flu-like symptoms (10% n=3) and nausea/vomiting (10% n=3).

Similarly, most caregivers reported the person did not experience side effects (36% n=34). The most common side effects caregivers reported observing were nausea/vomiting (9% n=9), dizziness (9% n=9) and confusion (6% n=6).

Patients reported that dizziness was the side effect most difficult to tolerate (31% n=6). Other side effects reported to be difficult to tolerate were vision changes (10% n=2), difficulty walking (10% n=2), changes in heart rate/chest pounding (10% n=2) and nausea/vomiting (10% n=2).

Caregivers reported that confusion (8% n=7) and nausea/vomiting (8% n=7) were the side effects most difficult to manage in the person they supported. They also reported that cough (6% n=5), dizziness (6% n=5), and changes in heart rate/chest pounding (3% n=3) were also difficult to manage in the person they supported.

5. Improved Outcomes

Patients reported that the most important outcomes of a treatment were maintaining the ability to think clearly (90.63% n=32) followed by preventing memory loss, maintaining quality of life, slowing the worsening of symptoms and maintaining the ability to care for themself.

Caregivers reported that the most important outcomes of a treatment for the person were slowing the worsening of symptoms (93% n=94) followed by maintaining the person's quality of life, maintaining the person's ability to think clearly (reducing confusion), preventing memory loss of the person and maintaining the ability of the person to care for themselves.

The Alzheimer Society of Canada asked patients and caregivers to evaluate the importance of different outcomes for their treatment or the treatment of the person they support, on a scale of 1 (not important) to 5 (very important).

Most Important Outcomes for Patients

Importance of outcome	1 - not important	2	3	4	5 – very important	Average
Slowing the worsening of symptoms	3.13% 1	3.13% 1	0.00% 0	9.38% 3	84.38% 26	4.69
Managing side effects of the medication	6.45% 2	12.90% 4	22.58% 7	12.90% 4	45.16% 14	3.77
Maintaining the ability to care for myself	3.23% 1	3.23% 1	0.00% 0	9.68% 3	83.87% 26	4.68
Preventing memory loss	3.03% 1	0.00% 0	6.06% 2	3.03% 1	87.88% 29	4.73
Maintaining my ability to think clearly (reducing confusion)	6.25% 2	0.00% 0	3.13% 1	0.00% 0	90.63% 29	4.69
Reducing disorientation (getting lost)	6.25% 2	0.00% 0	12.50% 4	12.50% 4	68.75% 21	4.38

Maintaining emotions	3.33% 1	3.33% 1	16.67% 5	10.00% 3	66.67% 20	4.33
Maintaining quality of life	3.33% 1	0.00% 0	3.33% 1	6.67% 2	86.67% 26	4.73
Ability to work	35.71% 10	14.29% 4	17.86% 5	7.14% 2	25.00% 7	2.71
Ability to sleep	3.57% 1	0.00% 0	3.57% 1	21.43% 6	71.43% 20	4.57
Ability to drive	17.24% 5	3.45% 1	6.90% 2	13.79% 4	58.62% 17	3.93
Ability to perform household tasks	3.45% 1	3.45% 1	17.24% 5	27.59% 8	48.28% 14	4.14
Ability to care for others who depend on me	20.69% 6	6.90% 2	10.34% 3	20.69% 6	41.38% 12	3.55

Most important outcomes for caregivers

Importance of outcome	1 - not important	2	3	4	5 – very important	Average
Slowing the worsening of symptoms	1.98% 2	0.00% 0	0.00% 0	4.95% 5	93.07% 94	4.87
Managing side effects of the medication	1.03% 1	2.06% 2	29.90% 19	29.90% 29	47.42% 46	4.21
Maintaining the ability for the person to care for themself	3.00% 3	1.00% 1	6.00% 6	13.00% 13	77.00% 77	4.60
Preventing memory loss of the person	3.00% 3	1.00% 1	5.00% 5	10.00% 10	81.00% 81	4.65
Maintaining the person's ability to think clearly (reducing confusion)	1.00% 1	0.00% 0	8.00% 8	6.25% 6	86.46% 83	4.77
Reducing the person's disorientation (getting lost)	4.17% 4	0.00% 0	7.29% 7	17.00% 17	71.00% 71	4.51

Maintaining the person's emotions	0.00% 0	2.00% 2	6.00% 6	20.00% 20	71.00% 71	4.62
Maintaining the person's quality of life	0.00% 0	0.00% 0	0.99% 1	7.92% 8	91.09% 92	4.90
Maintaining the person's ability to work	41.84% 41	10.20% 10	25.51% 25	8.16% 8	14.29% 14	2.43
Maintaining the person's ability to sleep	3.09% 3	4.12% 4	19.59% 19	24.74% 24	48.45% 47	4.11
Maintaining the person's ability to drive	37.76% 37	7.14% 7	18.37% 18	14.29% 14	22.45% 22	2.77
Maintaining the person's ability to perform household tasks	13.86% 14	12.87% 13	25.74% 26	23.76% 24	23.76% 24	3.31
Maintaining the person's ability to care for others	39.39% 39	16.16% 16	20.20% 20	12.12% 12	12.12% 12	2.41

Respondents were also asked if they would be willing to tolerate new side effects from therapies that can delay disease progression as well as therapies that can reduce symptoms. On a scale of 1 (will not tolerate side effects) to 5 (will tolerate significant side effects), 29% (n=9) or respondents said they would tolerate new side effects for therapies that can **delay the progression** of Alzheimer's disease and mild cognitive impairment. 36% (n=12) of respondents said they would tolerate new side effects for therapies that can **reduce the symptoms** of Alzheimer's disease and mild cognitive impairment.

If patients had access to a medication that delays the progression of Alzheimer's disease or mild cognitive impairment, these are some examples as to how this would impact their lives:

- "Give me more years of independent living. I have told my family that when I cannot live independently, I want MAID."
- "It would give me a chance to continue to have a life and fully participate in my life with my children and husband. It would delay my becoming dependent on others for my care."
- "It would mean everything. My boys are under the age of 12, and every moment together counts."
- "It could prolong normalcy in my life."
- "It would be important so that I could continue to drive and travel and care for my home and myself and my family."
- "Give some hope. Positive impact on my daily life."

Accessing a medication that delays the progression of Alzheimer's disease or mild cognitive impairment of the person someone cares for would impact caregivers in a variety of ways too. Here are some examples:

- "Knowing I've got more time with them."
- "It would lessen or delay caregiving responsibilities, as [I] already have others to care for."
- "At this stage, slowing the progression would not impact the care I already provide, but would help maintain some quality of life for my partner and myself."

- “More time to prepare for the future, adjust with the changes.”
- “Reduce stress, better quality of life.”
- “This would potentially allow them to continue living at a certain level of independence. In addition, it would alleviate some of the anxiety they are experiencing in relation to their diagnosis.”
- “Some independence for both of us, sharing household load, social interaction.”
- “This would allow the person living with dementia to maintain their abilities and independence for a longer period of time, which is significantly important for both the person and their care partner. This, however, would need to be balanced with potential side effects of the medication, as well as ongoing assessment, diagnostic testing, and availability of testing equipment.”
- “It would mean he would be able to do things without having to constantly ask me what we are doing that day. He would be able enjoy his day to day life more.”
- “I can't imagine it would help. The rate of progression is so staggeringly fast and she has already lost so much basic function.”
- “I would not agree to a medication that slowed the disease it needs to cure the disease.”
- “Of course, it would have been a lot easier on me! It is extremely important to try to slow down this horrific disease. It totally destroys the person! it's extremely sad to watch someone so vibrant, fade away and forget everything! Please try any drug that might help!!!”
- “It would mean that long term care may not be the only viable option.”
- “Slowing the progression of impairment would have allowed more time for thoughtful and informed advance care planning, arrangement of supports and transition to care at a comfortable pace (rather than on an emergency basis due to rapid disease progression). This would reduce anxiety and worry of family members and caregivers and improve overall quality of life for the entire family unit.”
- “It would give us quality days instead of quantity.”

6. Experience With Drug Under Review

We did not get enough responses from individuals who had experience with the Leqembi to provide many insights, however, here are some of the responses.

7 respondents with Leqembi (lecanemab) treatment experience completed the surveys - 4 patients and 3 caregivers. These respondents are from Ontario and Nova Scotia.

1 patient has early-stage Alzheimer’s disease and 3 patients either did not answer or did not know.

1 caregiver provided care to a person with early-stage Alzheimer’s disease, and 2 caregivers did not know.

3 patients were diagnosed in 2020 or earlier, and 1 did not know. For caregivers, they provided care for people diagnosed in 2019 or earlier.

3 of the patients had taken the medication Aricept in the past, both having negative experiences with this drug. 1 patient had also taken Exelon (rivastigmine) and Namenda (memantine), with memantine being the only drug they still take.

Patient Experience of Leqembi Treatment

No patients had no trouble accessing Leqembi (lecanemab) and 2 caregivers had no trouble having the person they care for access Leqembi.

Quality of Life of Leqembi Treatment

Patients and caregivers with lecanemab treatment experience who completed our survey chose to participate in the Leqembi (lecanamab) to “slow the progression of memory loss and hopefully provide a benefit to others who experience similar memory loss.”

All patients responded that taking Leqembi did not impact their daily life in any way.

Caregivers responded that the person they care for taking Leqembi affected their daily life in the following ways:

- “It helped maintain the quality of life of the individual.”
- “It meant a visit to the clinic every 2 weeks for the infusion until last year when they started auto injections weekly.”
- “It took most of a day every 2 weeks to take [the person] to [their] infusion clinic, plus a few additional days every year for testing purposes.”

1 patient found that Leqembi delayed the progression of their Alzheimer’s disease or mild cognitive impairment. 1 patient was unsure if Leqembi delayed the progression of their Alzheimer’s disease or mild cognitive impairment.

1 patient found that Leqembi slowed the worsening of symptoms of their Alzheimer’s disease or mild cognitive impairment. 1 patient was unsure if Leqembi slowed the worsening of their symptoms.

2 caregivers found that Leqembi delayed the progression of Alzheimer’s disease or mild cognitive impairment in the person they care for. 1 caregiver was unsure if Leqembi delayed the progression of Alzheimer’s disease or mild cognitive impairment in the person they care for.

2 caregivers found that Leqembi slowed the worsening of symptoms of Alzheimer’s disease or mild cognitive impairment of the person they care for. 1 caregiver was unsure if Leqembi slowed the worsening of symptoms of Alzheimer’s disease or mild cognitive impairment of the person they care for.

Caregiver comments:

- “As evidenced by standardized [assessment] tools.”
- “No way to know where we would be without. All tests and MRIs show the disease is still moving forward in the brain.”
- “At least subjectively, [the person’s] decline has been much slower than several other people I have known with a similar diagnosis (2 of whom have died).”

Caregivers reported some changes to their daily life as a caregiver, as a result of the person they care for taking Leqembi:

- “Our relationship and my ability to support the individual remains steady and I’m not sure that will continue with ongoing memory loss.”
- “Gave some hope for improved living with the disease.”
- “[Them] taking lecanemab only affected me by the time commitment [for transportation.]

Caregivers also reported how the person they support taking Leqembi affected their experiences as a caregiver:

- “Probably made my life easier and delayed the inevitable.”
- “No [affect.]”
- “It has made my life much easier (that may change over time, of course).”

Overall assessment

The following are some positive experiences patients had with taking Leqembi:

- “It has slowed memory loss (based on standardized assessments).”
- “Nothing changed. Made great friends at the clinic.”

The following are some positive experiences caregivers had with the person they care for taking Leqembi:

- “Slowed memory loss.”
- “No known positive experiences as we do not know where we would be without.”
- “The decline has been much slower than anticipated. The staff at the clinic have been exceptionally welcoming, friendly and supporting. It is not like going to the doctor.”

Patients and caregivers had no negative experiences with taking Leqembi.

7. Companion Diagnostic Test

N/A

8. Anything Else?

All patients and caregivers would recommend Leqembi to other people with Alzheimer's disease or mild cognitive impairment due to Alzheimer's disease.

Patient comments associated with the above statement:

- "Because of benefits to me and benefits to others as demonstrated through the results of the clinical trials."
- "Maybe once more is known. No real reason not to try it."

Caregiver comments associated with the above statement:

- "It may help them but to date we have had no side effects."
- "It will probably extend the person's ability to lead a reasonable life."

General comments from caregivers:

- "[The person I care for taking Leqembi] has been a very positive experience as the support has been phenomenal since the start at the clinic."

General feedback from people affected by dementia

Below is general feedback gathered (prior to the **Leqembi** surveys) about treatment/medication needs and issues, and health-care system use of people affected by dementia.

Medication costs

It is important to take into account the financial strains that many caregiver of people with dementia experience. The following information may be helpful to consider, when thinking about the importance of accessing affordable treatments.

In our analysis of the interviews [The Impact of First Link® across Canada Report, 2023], it became clear that one of the major factors impacting the quality of life of caregivers is finances. Those that were living with financial security (e.g. secure housing, food security, **ability to afford medications**), and in particular those who were able to afford private care (e.g. private homecare support, adult day programs, higher-end assisted living), described a **significantly higher quality of life than those that were living in poverty,** despite the same level and quality of services being offered by the Alzheimer Society (Alzheimer Society of Canada, 2023, p. 52).

Interviewed key stakeholders identified a number of resources and supports that are either limited or not available, but that would improve the quality of life and/or care of persons with dementia and their caregivers; these **included improved coverage from the Ontario Drug Formulary so that all relevant medications are covered and everyone has equal access to medication** (Alzheimer Society of Canada, 2010, p. 101).

Medication side effects/health-care system use

Some people with dementia will experience side effects from medications that can send them to hospital emergency rooms. This information may be helpful when thinking about some of the risks that may come with new treatments.

A number of participants indicated that the person they cared for attended the emergency room due to a fall, several due to **medication side effects** or issues, and several due to extreme behavioural issues that the caregiver could not manage (Alzheimer Society of Canada, 2023, p. 58).

About 44% of participants reported an emergency department visit within the last year, which is nearly double the 2015 CIHI population estimate from 2015 of 25% emergency room usage among dementia patients (Alzheimer Society of Canada, 2023, p. 10).

Approximately 28% of participants reported at least one overnight stay in hospital within the past year, which is higher than the 20% reported in the dementia population by CIHI in 2015 (Alzheimer Society of Canada, 2023, p. 11).

Benefits of medication/treatment

It was noted that further **cognitive decline can be delayed or stalled with the introduction of medication** (cholinesterase inhibitors) as well as the support provided to caregivers. This **allows persons with dementia to live independently longer and caregivers to provide care at home as long as possible**. (Alzheimer Society of Canada, 2010, pg. 66).

If treatments are able to allow people with dementia to live at home for longer, this brings many benefits. For example, this would save governments in Canada money, having less people living in long-term care homes. This would also benefit the person with dementia, as they can stay in an environment, they are comfortable in for longer. Finally, this would also benefit the people who provide care for the person, such as family or friends, as they would get to spend more good quality time with the person with dementia.

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.

N/A

1. 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.

   Some Leqembi (lecanemab) clinical trial locations in Canada shared the surveys with their clients.

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.

N/A

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

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: Luca Pisterzi
Position: Vice President, Research
Patient Group: Alzheimer Society of Canada
Date: June 17th, 2024

References

Alzheimer Society of Canada. (2023). *The impact of First Link® across Canada: Results of the Alzheimer Society of Canada's First Link caregiver survey and interviews*.

Alzheimer Society of Canada. (2010). *First Link demonstration Project: final evaluation report*.

Canadian Institute for Health Information. (2018b). *Unpaid caregiver challenges and supports*.

Cipriani, G., Lucetti, C., Nuti, A., & Danti, S. (2014). Wandering and dementia. Psychogeriatrics, *14(2), 135–142.*

National Institute on Aging. (2017, May 17). *Managing personality and behavior changes in Alzheimer's*.

Nimmons, D., Manthorpe, J., West, E., Rait, G., Sampson, E. L., Iliffe, S., & Davies, N. (2023). Views of people living with dementia and their carers on their present and future: a qualitative study. *BMC Palliative Care, 22(1), 38–38*.

Name of Drug: Lecanemab (Leqembi®)

Indication: Treatment of Alzheimer's disease

Name of Patient Group: Alzheimer Society of Ontario

Author of Submission: Kyle Fitzgerald, Director of Public Policy and Government Relations, Alzheimer Society of Ontario

1. About Your Patient Group

The Alzheimer Society of Ontario represents a federation of 26 frontline community support service providers, operating in every community across Ontario, and is part of a national federation of Alzheimer Societies across Canada. We supported over 75,000 clients last year, including both care partners and people living with dementia. We provide education and training to physicians and other health care professionals, as well as to the general public, and work to reduce the stigma that is far too often associated with dementia. As a health service provider, we offer system navigation, care partner respite, adult day programs, therapeutic recreation, and so much more at little or, for nearly all of our programs, no cost to families. With hundreds of staff and thousands of volunteers we seek to alleviate the personal and social consequences of Alzheimer's disease and other types of dementia, and to promote research into a cure. Learn more and find an Alzheimer Society near you: https://alzheimer.ca/on/en/about-us/find-your-local-alzheimer-society

2. Information Gathering

Two in-person focus groups were held, the first in Whitby, Ontario on February 6, 2024, the second in Toronto, Ontario on March 14, 2024. Both focus groups were hosted at Alzheimer Society offices. The Whitby focus group included seven participants (four care partners, three individuals living with Alzheimer's disease) who had direct experience with Alzheimer's disease, but were not involved in a clinical trial for lecanemab. The Toronto focus group was co-hosted by the Alzheimer Society of Ontario and the Toronto Memory Program, a clinical trial site for lecanemab. It included five participants (one care partner, one person living with mild cognitive impairment due to Alzheimer's disease, three people living with Alzheimer's disease), all of whom had personal experience with lecanemab. Participants had experience with two of the three drugs approved for prescription for Alzheimer's disease in Canada and publicly funded in Ontario, being Aricept (donepezil) and Reminyl ER (galantamine).

Participants were asked to self-report their connection to Alzheimer's disease, including diagnosis (if any). All participants in the Toronto focus group who were receiving lecanemab had a confirmed diagnosis to verify eligibility to enroll in the clinical trial. Participants in the Whitby focus group did not necessarily have a confirmed diagnosis (being differentiated from a probable diagnosis, which is given without confirmation of amyloid plaque presence in the brain); their feedback is nevertheless seen as of equal importance, due to their interactions with health care providers being more typical to what Canadians will experience should the drug being considered be approved for use outside of a clinical trial environment. Participants with later-stage Alzheimer's disease, who would not be eligible for the drug being considered, also bring firsthand experience of disease progression and are thus able to speak to the importance of delayed progression—the desired outcome of lecanemab.

Participant ages ranged from 66 to 89. Six participants were male and six female.

Participants in both focus groups were asked a series of questions, included as Appendix B. Both focus groups were recorded to ensure participant sentiment was accurately captured in this submission. Participants received a $25 gift card as thanks for their time; this was presented to all participants regardless of their feedback. The Alzheimer Society of Ontario also offered to reimburse expenses associated with attending the focus groups; no participants requested reimbursement.

3. Disease Experience

Focus group participants were unanimous in declaring Alzheimer's disease has upended their day-to-day lives, disrupting retirement plans and redefining their relationships. Of particular concern was the lack of predictability, with multiple participants citing lack of

knowledge of what was to come as a concern (a theme that continued into later questions relating to what a disease-modifying treatment could address).

Participants felt robbed of time, with care partner participants sharing emotional stories of, in their eyes, losing their spouse far too early. One focus group spoke at length about travel plans that were made and never realized: care partners and participants living with Alzheimer's disease shared how they had planned to enjoy their "golden years" with trips that had been put off for years, and will now never happen.

Both care partners and participants living with Alzheimer's disease reported a change in how others approached them, ranging from isolation to paternalism and a perceived inability to be independent. While participants noted Alzheimer's disease does result in a gradual loss of ability to independently perform activities of daily living, several complained of no longer being seen as an independent person. One participant shared that they have neighbours who expect them to fall every time they leave their home, and will "hover" nearby expecting this result. Participants also noted a lack of available support, with care partners feeling bound to their home due to unavailability of services to support people living with dementia in their desire to age in the community.

A lack of control was noted by numerous participants. Some who reported taking currently-approved, non-disease-modifying treatments for Alzheimer's disease said they did so to feel as if they were at least doing something.

The words of participants themselves best summarizes their experiences with Alzheimer's disease. All names have been changed for quotes throughout this submission.

> "Day-to-day I feel very kind of tied down, not able to go anywhere, or participate in anything unless it's Alzheimer's related. My whole life is all Alzheimer's all the time." Care partner to husband living with Alzheimer's disease.
>
> "The neighbour on the street is waiting for me to drop. I'm really sad about that." Person living with Alzheimer's disease.
>
> "We have neighbours on the street who walk continuously. And because they know she has memory loss, they are careful with her in the assumption she may fall because of the memory loss. They're always watching her. They hover." Care partner.
>
> "I can leave her alone for a few hours […] I am restricted a lot compared to before she had the disease." Care partner to wife living with Alzheimer's disease.
>
> "I still have discussions with him, I just don't have that partner relationship with him. He is no longer able to do a lot of things. He's lost concept of time." Care partner to husband living with Alzheimer's disease.
>
> "I hate it, hate it, hate it." Person living with Alzheimer's disease.
>
> "I had a very kind of high-level job, [redacted], and when I was 60 I decided that perhaps it may be affecting my abilities to carry out my responsibilities. So I retired and I think for quite a while I had been asking doctors for some kind of diagnosis or help. And basically nobody could help me or make a diagnosis and so finally I went to the Toronto memory clinic and they did." Person living with Alzheimer's disease.
>
> "I took early retirement to stay home with my husband. That has financial implications. We sold some property we had, in order to [retire early]. Our retirement plans are completely out of the window. He's not really able to travel. And so, all those air miles that I collected, hotel points and everything are … you know... It's a real shame." Care partner to husband living with Alzheimer's disease.
>
> "It robs you of having someone who you love to go travel with you. The other big change is it is very, very stressful on caregivers." Care partner to wife living with Alzheimer's disease.
>
> "What I find hard, because Ted functions very well, where he struggles it's remembering the exact word like "pass me the, you know the thing in the coffee, the cup". It takes him a minute to come up with the word. And the other thing is, sometimes if we haven't seen somebody for a long time, he recognizes the face but can't remember the name. But because he functions fairly well about 90% of the time, I lose patience because I forget that there's a memory issue." Care partner to husband living with Alzheimer's disease.

4. Experiences With Currently Available Treatments

Participants had experience with Aricept (donepezil) and Reminyl ER (galantamine). These medications, among other cholinesterase inhibitors, aim to reduce symptom severity but their effects are temporary and do not stop or fix damage caused in the brain by Alzheimer's disease. Despite treatments currently being available for prescription for Alzheimer's disease, these are not comparable in outcome to the drug being considered which would alter the clinical progression of Alzheimer's disease.

Those with experience accessing one of the above drugs reported difficulty quantifying their benefit, if any. Participants deferred to the advice of medical practitioners, with one person living with Alzheimer's disease reporting he was prescribed Aricept with little explanation of its possible benefits. Another participant said he "went along with it" when his doctor offered a prescription.

Recipients of both Aricept and Reminyl reported no noticeable benefits, again expressing difficulty judging if their or their supported person's cognitive decline was lessened by the drug being prescribed. One participant offered that her cousin is prescribed Aricept and sees it as a "band-aid" and a "happy pill", also adding a lack of noticeable benefit. One care partner whose husband takes Reminyl said she "hasn't seen any difference, no side effects".

Three participants, two with experience with Aricept and one with Reminyl, strongly agreed with each other's sentiments: all had at least six months' experience with the respective drug, all reported "high hopes" initially, none had observed any side effects (one participant noted a low dose of Aricept had been prescribed due to the prescribing physician's concerns around side effects), and on observed benefits the two participants receiving Aricept reported none, while the participant with experience of Reminyl (a care partner) said she had seen a "slow decline" in her husband's condition.

The knowledge of participants, and of their medical providers, around available treatments differed widely. One person living with mild cognitive impairment said he was unaware of treatment options before being enrolled in the lecanemab clinical trial. Care partner participants reported a need to educate their doctors, with two noting pushback from medical providers when advocating for their supported person: one care partner reported her concerns of her husband's memory loss were dismissed as "the result of the stress of Covid", and another reported her doctor telling her husband, "oh you're just getting old". Care partners reported physician knowledge of Alzheimer's disease is limited, with a need for patients to advocate for themselves or their supported person. Detection and diagnosis emerged as a barrier to accessing current treatment options.

No participant reported existing treatment options meeting their needs. Participants felt compelled to try any option, and in the absence of negative side effects the prevailing attitude was that something is better than nothing. The words of one care partner participant in Whitby fairly represent participant views: "You expect to see some positive change, but one hasn't seen any positive change from the perspective that there is no cure for this disease, so why are you taking this in the first place? But it's prescribed, so…"

5. Improved Outcomes

Participants expressed a unanimous desire for a cure, or disease-reversing treatment, signalling the importance of further research to meet patient need. In the absence of a disease-reversing treatment, participants expressed a desire for a disease-modifying treatment: a drug that can slow the clinical progression of Alzheimer's disease, which is not currently available in Canada. In the words of one care partner supporting her husband living with Alzheimer's disease: they would like "something that reverses Alzheimer's disease, but also helps with a slow decline." Another participant agreed, expressing hope that their Alzheimer's disease would be "not getting worse, and it's stable." A participant living with Alzheimer's disease and enrolled in a lecanemab clinical trial noted the drug has slowed her cognitive decline, adding that: "much more desirable would be something that could actually improve things", referring to a partial reversal of symptoms of Alzheimer's disease. Summing up the desire for a cure, coupled with optimism around a disease-modifying treatment, one participant noted: you "always want to have "perfect", [but you] take something that gives you 90%."

Trade-offs that participants would need to consider can be grouped into three categories: time, cost, and side effects. Some participants expressed reluctance to structure their life around an infusion schedule, with one care partner saying her and her supported person's decision would consider "how often you would have to take it." Participants were also concerned that a disease-modifying treatment may not be funded for all eligible Canadians, with one participant noting that he "couldn't do something that is cost prohibitive." Participants also expressed a strong desire to make an informed choice with respect to risks of side effects, with

one participant saying she would want to know “if there are negative interactions with existing medications” and, if there are, would then need to also consider the added risk of stopping or changing that existing prescription.

When evaluating risk and trade-offs, participants said they would have more confidence with easy access to trusted sources of information. Some participants said they would like to consult with multiple medical providers for their opinions. Overall, there was a desire amongst participants for clear communication: in the words of one participant, “Is it going to help me? Is it going to reduce any pain I have, or mental loss? It’s something I really need to know. Is it going to make me better?”

6. Experience With Drug Under Review

All participants with direct experience with lecanemab accessed it through a clinical trial at the Toronto Memory Program.

Only one of the four participants with direct experience receiving lecanemab through the clinical trial reported noticeable negative side effects. This participant reported fatigue and shaking while receiving an infusion of lecanemab, a side effect that was resolved by lengthening the duration of infusion sessions. The side effects did not repeat during subsequent infusions.

Participants reported positive experiences with lecanemab. One person living with Alzheimer’s disease said of the positive impact she has observed: “I can focus better, my mind is clear.” This general sentiment was broadly similar for all participants with experience receiving lecanemab: none reported it reversed symptoms or produced radical results, however all noticed either no decline in cognitive function or mild improvements.

Continuing a theme identified during discussion of gaps not filled by currently available treatments, participants noted a feeling of empowerment that a disease-modifying treatment was available to them. Said one participant: “I feel positive and empowered by doing this [participating in the clinical trial]. I take very good care of myself. I was happy and relieved to be living my life normally, having a full life, knowing that I’m not getting worse was really enough for me.”

While participants could not, nor could they be expected to, determine to what extent lecanemab altered the clinical progression of their Alzheimer’s disease (especially in cases where lecanemab was administered alongside currently approved non-disease-modifying drugs), there was a self-observed consensus that taking the drug halted or slowed cognitive decline, with one participant observing: “I have not got[ten] worse, so I think that’s a very positive impact.”

Participants differed in their attitude towards the trade-offs necessary to participate in the lecanemab trial. As an infused product, participants had a choice of making bi-weekly visits to an infusion centre, or using an auto-injector. One participant noted access to the self-administered auto-injector made “a very big difference”, saying his infusion centre was a one-hour drive away in addition to a minimum of two hours at the infusion site. The participant made explicit reference to improved quality of life as a result of using an auto-injector.

Conversely, a care partner to her husband living with Alzheimer’s disease stated that they declined an auto-injector when it was offered, saying the infusion sessions had become “a part of [their] social weekend”, offering “social time” with staff and fellow patients.

At various times during both focus groups, patients raised the considerations of ease of access, cost, and anticipated benefit as factors that they would consider, and would like national regulators to also consider. One participant also noted: “I think it’s critical that there be some kind of assessment of the kind of relative performance of the drugs. I can’t speak to the other drugs because I have no experience with them. But I do think that this one is beneficial and if it’s beneficial, it must have the impact of lowering total medical cost borne by the system. So if we can conclude that it has been effective in keeping the symptoms at bay then I think that’s priceless or at least very cost-effective for the kind of costs involved versus incremental medical costs being incurred by the system.”

7. Companion Diagnostic Test

Lecanemab requires confirmation of amyloid plaque buildup in the brain prior to commencement of treatment. For the near future, this necessitates one of two procedures: a PET scan, or a lumbar puncture followed by cerebrospinal fluid analysis. Participants were asked about their experiences, if any, with these two procedures. While not required for diagnosis, MRI scans are indicated for monitoring; some participants volunteered experiences with these scans as well.

This was the area with the greatest divergence between participants with experience receiving lecanemab, and those without. Participants receiving lecanemab reported positive experiences with diagnostic procedures, with one person living with Alzheimer's disease saying her experience receiving both PET and MRI scans has been "easy as pie". Another participant received a lumbar puncture, and expressed neither strong positive nor negative feelings about the experience. No participants paid for the procedures, however PET scans and lumbar punctures/CSF analysis for the purposes of diagnosing Alzheimer's disease are not publicly funded in Ontario: patients not involved in clinical trials would need to pay out of pocket for diagnostic tests, or have them covered by other sources, without policy change in Ontario. This was noted by one participant, who said he was aware that outside of a clinical trial he had the option to "pop across the border over to the U.S.".

Participants not involved in a clinical trial reported a lack of awareness of diagnostic options, and a lack of conversation about these procedures with medical providers. There was confusion among participants who had received a test, but did not know for what: multiple participants mentioned a "brain scan" but did not know if it was a PET scan, and for what purpose the test was conducted. Some participants were unaware diagnostic tests, beyond cognitive assessments, existed, and reported no proactive discussion with their primary care provider; one participant surmised that his doctor did not want to "cause confusion".

Were a diagnostic procedure to be required to access treatment, participants raised a number of concerns they would need to be addressed before consenting: what preparations, if any, are necessary; "is it painful?"; and what risks are involved, with one participant asking "can they hit a nerve, or are there any risks" associated specifically with lumbar punctures.

Participants expressed preference for less invasive procedures, though this was clarified to be a preference rather than a requirement: one participant said he "want[ed] the perfect solution, but if I can't get it I will settle for what is available." Another participant stated she would prefer a PET scan but would, if necessary, agree to a lumbar puncture.

Participants expressed a strong desire for medical advice on diagnostic procedures, with one participant noting her decision would be based on the information received from care providers. Another stated a second opinion would give her more confidence.

The differing levels of knowledge between participants of both focus groups highlights the varying degrees of knowledge practitioners have about dementia care, and their subsequent willingness to discuss treatment options with patients. Participants connected to the Toronto Memory Program, a clinic with specialised knowledge in dementia care, were well informed and confident about their treatment options. Those not connected to the Toronto Memory Program reported less confidence and awareness of available procedures.

8. Anything Else?

The Alzheimer Society of Ontario wishes to emphasise, on behalf of the clients we have the honour to serve, the unmet need that the drug under review fills for Ontarians and Canadians living with Alzheimer's disease. No other product available in Canada can alter the clinical progression of Alzheimer's disease, the single most important unmet need expressed by focus group participants. A treatment for Alzheimer's disease, of which there are four approved in Canada, cannot be compared to a disease-modifying treatment, of which there are none: the ability to retake control, to regain time, to fight back against this horrible disease has long been hoped for by Canadians affected by dementia. That possibility is now within reach.

> "I've been following lecanemab in the States and the approval process and so forth. The U.S. and Japan use it, so let's not delay it further. **I feel like I'm not just impatient, I feel desperate.** I would do anything as far as the PET scans, the cost, the treatment time, any of those are surmountable if it would actually bring my husband back. He's probably past being a candidate now…he's probably past. But, there are others. So, **do it now**." Care partner to her husband living with Alzheimer's disease.

Appendix A: 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.

Yes. The Toronto Memory Program led recruitment of participants for the Toronto focus group, with all participants also being associated with the Toronto Memory Program. The Alzheimer Society of Durham Region, which is a legally distinct entity from but part of the same province-wide federation as the Alzheimer Society of Ontario, hosted and recruited participants for the Whitby focus group.

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

   No.

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

Table 1: Financial Disclosures

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

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Biogen Canada				X
Eisai Canada				X
Eli Lilly Canada				X
Novo Nordisk Canada				X
Roche Canada				X
Ministry of Health, Ontario				X
Ministry for Seniors and Accessibility, Ontario				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: Kyle Fitzgerald
Position: Director, Public Policy and Government Relations
Patient Group: Alzheimer Society of Ontario
Date: May 30, 2024

Appendix B: Questions Asked to Focus Group Participants

Participants in the Whitby, Ontario focus group were asked the following questions:

1. Describe your connection to, and experience with, Alzheimer's disease. How has it changed your life? In what way(s) have you found it to be most impactful?
2. There are three medications funded for treatment of Alzheimer's disease in Ontario: Aricept (donepezil), Reminyl ER (galantamine), and Exelon (rivastigmine). A fourth, Ebixa (memantine), is approved for use in Canada but not publicly funded in Ontario. Thinking only of these four currently available treatments:

    a. Do you have any direct experience with them? If so: have you noticed any improvements and/or side effects? If not: were there any barriers (cost, access, etc) that prevented you from accessing them?
    b. Did your health care provider(s) mention treatment options to you, and/or did you research them yourself? Do you feel existing treatment options meet your needs, or are there gaps?
3. What is, to you, the most important outcome not offered by currently available treatments?
4. Thinking of the outcome(s) you mentioned in the last question, how would your life change if there were a treatment available that could offer this? What risks would you take and what trade-offs would you make (such as acceptable side effects, time to access the treatment, etc) to get this outcome?
5. Still thinking of the same outcome(s), what else would you consider when deciding whether or not to access a treatment that might offer this?
6. The drug being considered, lecanemab, requires a confirmed diagnosis of mild cognitive impairment or early Alzheimer's disease. This diagnosis can currently only be obtained in Canada through a PET scan or a lumbar puncture, followed by CSF analysis (a lab test). Do you have any experience with one or both of these diagnostic tests? If so: how easy or difficult was it to obtain? Did you encounter any barriers, such as wait time or cost? Were you confident going in to the experience, or did you have unaddressed concerns? If not: were you aware that these options existed to seek a confirmed diagnosis? Did you discuss them with your care provider? Were there specific barriers that prevented or discouraged you from seeking a confirmed diagnosis?
7. Based on what you know today of PET scans and lumbar punctures, would you be confident and comfortable accessing one of these options if it was required prior to beginning treatment? Do you feel the results would give you more certainty before deciding on treatment options? What would you want to know about these diagnostic options before agreeing to proceed?
8. Is there anything else you would like the people who will decide whether or not Canadians have access to disease-modifying treatments for Alzheimer's disease to know? What values do you think are most important to be considered by those evaluating lecanemab?

In addition to the above eight questions, participants in the Toronto, Ontario focus group, who all had direct experience with lecanemab, were also asked the following questions:

1. During the time you were receiving treatment with lecanemab, what benefit(s) if any did you notice? How would you say these benefits impacted your life, and the lives of your family and care partner(s)?
2. During the time you were receiving treatment with lecanemab, what negative impact(s) if any did you experience? How would you say these negative impacts affected your life, and the lives of your family and care partner(s)?
3. During the time you were receiving treatment with lecanemab, what side effects did you experience if any? How did you manage these side effects?
4. Thinking back to any other medications you have tried that were prescribed for Alzheimer's disease, did you find lecanemab easier, about the same, or more difficult to tolerate? In what way(s)?

Name of Drug: Leqembi (lecanemab)

Indication: Lecanemab is indicated as a disease-modifying treatment in adult patients with Alzheimer's disease. Treatment with lecanemab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease

Name of Patient Group: Dementia Network Calgary

Author of Submission: Diane Rennie and Kim Brundrit

1. About Your Patient Group

Dementia Network Calgary is a growing group of knowledgeable, capable, and passionate individuals from across the public (including those living with dementia and their family caregivers), private and nonprofit sectors in Calgary and area with an interest in Alzheimer's disease and related dementias. Created in 2013, it is based on a collective impact model, an innovative approach to tackling complex social and systemic issues, which requires the coordinated efforts of cross-sector stakeholders. For more information, please visit: www.dementianetworkcalgary.ca

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

DNC engages with people with lived experience in several ways including: community gatherings, surveys, focus groups and a facebook group with over 1000 members. A purpose-designed survey specific to this submission was completed in May/June 2024. There were 91 respondents; seven were people living with dementia (6 females, 1 male with 4 being between 65-74 and 3 being between 75-84 years of age). Fifty care partners completed the survey of which six were male, 42 female and two preferred not to answer. The majority of the care partners were over the age of 55 with 36% being between the ages of 55-64.

The vast majority of our community are located in Calgary and the surrounding area, but some of the surveys reached a broader audience across Alberta and Canada. The demographics of community gatherings and focus groups are typically a mix of genders with adults between the ages of 30 and 85. Everyone who attends has lived experience with dementia either as a person with a diagnosis or as a caregiver/family member. We do not collect ethno-cultural data.

We have engaged with thousands people impacted by dementia over the last six years. Due to the nature of dementia, we consistently receive more engagement from caregivers than from people with a diagnosis. It can be very challenging for people with a diagnosis to complete surveys and participate in focus groups due to limitations with verbal expression and cognitive impairment.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and **quality of life**. Are there any aspects of the illness that are more important to control than others?

When asked about how dementia impacts their day-to-day life and quality of life, both people living with dementia and their care partners described the loss of independence, decreased ability to accomplish tasks that were once easy to complete as well as financial, physical and emotional stress and exhaustion. Providing care can impact all aspects of day-to-day life.

The following quotes paint a picture of the challenges:

“He has lost confidence in his ability to manage finances and behave appropriately in social situations so he relies on me to be there to fill in any gaps.”

“I’ve watched my mum’s progressive decline over the last few years and can see how quickly she reached the point of not being able to use the telephone, a tv remote, or do anything in the kitchen other than use the microwave for 30 seconds at a time. It feels like in a blink of an eye she went from being fairly independent to no longer being able to live alone.”

“My mother is afraid to be in social situations because she fears her ability to respond is impacted. She isolates herself and is becoming a shell of the person she once was.”

“It is shocking to see how MCI has impacted my sister and her family. In two short years she is no longer the capable family manager she once was. She now lives with fear and denial that there has been any change with her memory. She is defensive and will not accept that she cannot remember details. Her attitude has isolated her from family and friends who are concerned and want to help. I worry about her future and am so sad for her spouse and children who deal with her anger every day.”

“She has no independence whatsoever. She lives in a near constant state of fear, anxiety and paranoia.”

“It has meant I experience almost daily stigma and discrimination - and zero disability support to live independently apart from what I self manage.”

“He is quite dependent on me for cooked meals, remembering what he has to do each day, where to store things and where to find things, going to appointments with him, doing all our finances.”

“My mom is now in a care facility for Alzheimer’s. She is not the same person she once was - she ran a business with hundreds of employees, and now she can't even toilet herself. The declines have been so very sad, especially at the start when she could sense it was happening. It always scared her to have Alzheimer’s, so she kept saying "oh this scares me - I hope it's not that". She said this even after we were told she had Alzheimer’s. Basically everything that she had built her life to be has been taken away”.

“My father can’t do the things he loved to do such as grocery shop, garden, cook and eat delicious foods. He is now confined to a bed or chair watching tv or sleeping. He was active and vibrant, and always on the go. Now everything he does from walking to feeding himself to dressing to going to the toilet can no longer be done with privacy or dignity. He can no longer eat/chew the foods he loves to eat. He can no longer whip up gourmet meals with ingredients from his garden. He can no longer email his friends or do his online banking. He gets confused using the tv remote and the telephone. It’s heartbreaking to watch him struggle. His anger and frustration is palatable and understandable. He needs 24/7 assistance with all his life tasks. What kind of “life” is this? We enter the world with such flourish and fanfare, yet we leave the world joyless, without dignity.”

“Managing my parent's care, both personally and financially, is a strain physically and emotionally.”

“There is a loss of independence and personhood for both the person living with mild dementia and their care partner. Roles shift dramatically even in the early phases of disease detection and presentation.”

“I am always on call and never feel like I can truly relax. The calls come at anytime, day or night. I live with constant stress and anxiety and worried about what's going to happen next.”

“The disease took hold of my mother who was a very independent, outgoing individual. She at 85 began losing her memory, lost her ability to drive safely, was easily confused. She was diagnosed with Alzheimer’s at 88 years. I became her caregiver, monitoring her life to keep her physically and financially safe. I was devastated to see how the disease was taking away hers and my livelihood. I still, even with her being in a facility, visit with her daily.”“My children and my spouse don't get the best of me because I have no "best" left.”

“We can't go on vacation for more than 5 days and I'm always worried if my phone is out of sight.”

“I spend every day with my mother at her care home. It is heartbreaking.”

“Emotionally this disease is completely draining. Visits are hard, especially those as she continues to deteriorate.”

“I developed anxiety and depression due to exhaustion and mom's verbal abuse.”

“Day to day there is always a heaviness in knowing what is happening with our mom.”

“Loss of spousal relationship, time spent looking for lost items, doing tasks that were once his, accompanying him to appointments etc., ongoing frustration with having to repeat myself, loss of retirement plans and travel, financial concerns for the future, sadness and depression (now being treated for same).”

“My health has declined since her diagnosis, as a result of stress, putting her needs before mine. My quality of life has definitely deteriorated in terms of social involvement with friends and relatives. My physical capabilities too have dramatically changed since my mom’s diagnosis. I have not had the time, effort or desire to exercise like I used to or eat as well. My relationship with my husband has been tense since having to constantly look in on my mother.”

“I’m beyond exhausted, and I have no life outside of medical appointments, pharmacy runs, and trips to the grocery store. Friends and family do not understand the extent this level of care takes.”

“I’m afraid I’ll get in an accident or I’ll get sick, and then I won’t be able to provide care. I’m always in a state of being on the edge waiting for the next emergency or fire to be put out. My life is chaotic. I wouldn’t have it any other way if it means keeping my parents in their own home as they age.”

“It feels that all my physical and mental energy is drained by the end of the day. I wake up exhausted as it seems that I have to be on the alert even at night. I have no life of my own. Everything we do revolves around her dementia and Alzheimer’s.”

“I miss a lot of work now and when I do not work, I do not get paid.”

“I miss work at least once a week, often more. I pay out of pocket for private help and additional items like technology aids and special programs.”

“I have had to take a leave of absence from my job. I no longer have an income.”

“I am draining what little retirement savings I had worked for over the years.”

“There is always a part of my brain worrying about mom. During her diagnostic process, I missed at least a half-day of work, each week, for about 3 months, to get to appointments.”

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

We are unaware of any medications or treatments for dementia or MCI. Patients might be prescribed medications to manage symptoms (ex. Aricept). As a result, we did not hear from anyone who has access to a specific treatment for MCI or dementia.

A caregiver expresses frustration with the lack of treatment options: “My loved one now relies on things like posting reminder sticky notes all over the house and in her car so she can remember to do things like pick up more milk. Even though she is receiving medical care, nothing has slowed down her memory loss. We all pray for some type of treatment that can help her before it is too late.”

5. Improved Outcomes

CADTH is interested in patients’ views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

The lack of medical treatments for this disease makes it difficult for patients and caregivers to imagine “improved outcomes”.

When people living with dementia were asked about how daily life and quality of life might be improved by a new treatment or therapy, their comments were simply a “better quality of life” and “it would be greatly improved!”

A care partner summarized the importance of any medical treatment that might delay the progression of the disease as “the more time one could have with capacity is a gift.”

Additional comments included:

“improvement in the ability to diagnose and treat people living with mild dementia with confidence and competence”

“Any medication that is proven to be effective and safe would give me a feeling of hope that my children and my grandchildren will not have to live like I do as I care for two parents with dementia. In addition to the stress caused by caregiving, the worry about how to ensure that my children will never have to give up their lives to care for me is constant.”

“..the advancement of a medication that preserves memory, enables engagement, and extends independent function.“

“A medicine that combats the fidgeting and pacing associated with sundowning.”

When asked if there would be value in a treatment that would delay progression of the disease, the following comments were made:

“It would allow more enriched time with the person living with dementia as well as more time to prepare.”

“More years of better quality of life. Perhaps the individual might pass away from some other cause prior to dementia slowly stealing their life.”

“Personally, I would do anything to delay the progression of the disease if I were to be diagnosed. Because there is no "cure" and I've cared for 2 parents with dementia, I would choose to enact MAID, so any delay in disease progression would literally prolong my life.”

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

We have not engaged with anyone who has experience with the drug under review. Clinical trials for this treatment were not offered in Calgary.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.

- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

As per the previous question, we have not engaged with anyone who has experience with the drug under review. Clinical trials for this treatment were not offered in Calgary. Without knowing what companion diagnostic tests might be required, it's difficult to comment, other than to say that caregivers often need to attend these types of tests to ensure the person with the diagnosis is able to find their way, understand the process and provide consent.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

We would appreciate any feedback on our submission as this is the first time we have been involved in this process and we anticipate additional submissions in the future.

Appendix: Patient Group Conflict of Interest Declaration

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

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

   No

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

   No

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

Table 1: Financial Disclosures

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

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

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: Kim Brundrit

Position:Collective Impact Lead

Patient Group: Dementia Network Calgary

Date: June 15, 2024

Clinician Group Input

CADTH Project Number: SR0822-000

Generic Drug Name (Brand Name): Lecanemab

Indication: Alzheimer's disease

Name of Clinician Group: Canadian Consortium on Neurodegeneration in Aging

Author of Submission: Eric Smith, MD

1. About Your Clinician Group

The Canadian Consortium on Neurodegeneration in Aging (**CCNA**), a CIHR-funded network with collaborating partners such as the Alzheimer Society of Canada and Brain Canada, was formed in 2014 by more than 350 clinicians and researchers throughout Canada who came together to accelerate progress in research on age-related neurodegenerative diseases (ccna-ccnv.ca). CCNA's scientists are often referred to the key scientific experts and opinion leaders in all aspects of dementia research CCNA's leading vision is to significantly reduce the burden of age-related neurodegenerative diseases of Canadians by accelerating the discovery, innovation, and the adoption of new knowledge. We aim to position Canada as a global leader in increasing our understanding of neurodegenerative diseases, working towards prevention, and improving the quality of life of those living with dementia.

To achieve the CCNA's vision, it has been conducting high quality research to understand and prevent dementia as early as possible, and to improve the quality of life and care of those living with dementia while understanding the various related ethical, legal, and social issues. The CCNA works to effectively translate significant findings in order to reach out to the public, stakeholders, and people with lived experience, and disseminate knowledge to these various audiences. CCNA has received international peer review and been renewed by the Canadian government twice. It has now begun its phase 3 (2024-2029).

2. Information Gathering

In April 2024 the CCNA commissioned an initiative on Preparedness for Alzheimer Disease Modifying Therapies in Canada, to synthesize information on the Alzheimer's disease (AD) modifying therapies lecanemab and donanemab, with the goal of identifying gaps in knowledge about application of these treatments, preparedness of the Canadian health system, and areas for future investigation with an emphasis on research that will be most applicable to the Canadian health system. A Steering Committee was formed, and working groups were created to investigate clinical effectiveness, patient selection, subgroup effects, diagnosis and management of amyloid-related imaging abnormalities (ARIA), the number of potentially eligible patients by province, and equitable access to the potential benefits of therapy.

This clinician and researcher input to CADTH has been prepared by the CCNA Steering Committee for Canadian Preparedness for Alzheimer Disease Modifying Therapies. Input from the working groups of this initiative is expected by September 2024. The results of our initiative will be posted on the CCNA website, released to the public for comment, published on a preprint server, and submitted for publication in a Canadian peer-reviewed medical journal.

The information in this document is based on Canadian expert opinion, review of the CLARITY-AD trial publication and appendix (van Dyck CH et al. N Engl J Med 2023;388:9-21), CLARITY-AD trial protocol, a consensus state on appropriate use of lecanemab published by a group of American investigators (Cummings J et al. J Prev Alzheimers Dis 2023;10:362-377), a report by the RAND corporation on dementia care in Canada (Liu JL et al, RAND Research Report 2019), and a peer-reviewed publication on the preparedness of Canada for AD disease-modifying therapies (Black SE et al, Can J Neurol Sci 2023:1-8).

The Steering Committee is chaired by Dr. Eric Smith, MD, MPH, a dementia neurologist with expertise in vascular dementia and cerebral amyloid angiopathy. The Vice Chair is Dr. Howard Chertkow, MD, dementia neurologist the Scientific Director of the CCNA. Other Steering Committee members include Dr. Natalie Philips, PhD (neuropsychologist with expertise in cognitive assessment and diagnosis), Dr. Howard Feldman, MD (dementia neurologist and expert in designing and conducting trials for AD).

3. Current Treatments and Treatment Goals

AD is a progressive neurodegenerative disease that is marked by accumulation of senile plaques, composed of beta-amyloid, and neurofibrillary tangles, composed of aggregated tau.

Currently, there are two approved medication classes for AD in Canada: the cholinesterase inhibitors and memantine.

The cholinesterase inhibitors are donepezil, galantamine, and rivastigmine. These drugs act to increase the concentration of acetylcholine in the synapse. They are believed to have a cognitive enhancing effect, but do not modify the course of the disease. In other words, the rate of cognitive decline is not altered by these medications. Once treatment is stopped symptomatic benefits are lost. They do not have sustained benefits or significant evidence that they modify the underlying disease biology. Clinically, this class of drugs is felt to provide modest symptomatic effects. The primary outcome for trials of the cholinesterase inhibitors was the change in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). According to Cochrane reviews, treatment with cholinesterase inhibitors for six months “produced improvements in cognitive function, on average -2.7 points (95%CI -3.0 to -2.3), in the midrange of the 70 point ADAS-Cog Scale”. Cholinesterase inhibitors are covered by drug insurance programs for older Canadians, but most provinces require that a special authorization form be completed for their use. The Consensus Canadian Conference on Dementia Diagnosis and Treatment of Dementia (CCCDTD) guidelines, 4th edition, addressed the use of cholinesterase inhibitors, stating that they “recommend a trial of a cholinesterase inhibitor for most patients with AD (Grade 1A)” (Gauthier S, et al. Can Geriatrics Journal 2012;15:120-126).

The other medication approved by Health Canada for the treatment of dementia due to AD is memantine. Memantine blocks NMDA receptors. Like the cholinesterase inhibitors, memantine is thought clinically to have a modest symptomatic benefit in more advanced AD without modifying the course of the disease. According to a Cochrane systematic review, “high-certainty evidence from up to 14 studies in around 3700 participants consistently shows a small clinical benefit for memantine versus placebo: Clinical global rating (CGR): 0.21 CIBIC+ points (95% confidence interval (CI) 0.14 to 0.30); cognitive function (CF): 3.11 Severe Impairment Battery (SIB) points (95% CI 2.42 to 3.92); performance on activities of daily living (ADL): 1.09 ADL19 points (95% CI 0.62 to 1.64); and behaviour and mood (BM): 1.84 Neuropsychiatric Inventory (NPI) points (95% CI 1.05 to 2.76)” (McShane R, et al. Cochrane Database Syst Rev 2019;3:CD003154). Memantine is not covered by most provincial formularies, with the exception being Québec. Therefore, according to our expert knowledge this drug is not widely used in Canada. The Canadian Consensus CCCDTD, 4th edition, recommends that “combination therapy of a cholinesterase inhibitor and memantine is rational (as the medications have different mechanisms of action) and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B)” (Gauthier S, et al. Can Geriatr J 2012;15:120-126).

Some medications are used to off label to treat behavioural complications of dementia, including antidepressants and antipsychotics. However, these medications do not modify the course of AD.

Non-pharmacological treatments for dementia include supportive care, advance care planning, and cognitively stimulating therapies (such as art therapy and recreational therapy). However, none of these therapies have been shown to modify the accumulation of senile plaques and neurofibrillary tangles in AD.

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.

The main limitation of current pharmacological and nonpharmacological treatments for AD is that they treat symptoms but do not modify the course of the disease. The cholinesterase inhibitors and memantine improve cognition, as demonstrated by higher mean scores on the ADAS-Cog in clinical trials, but the rate of decline over the longer term is not altered. The lack of a disease modifying therapy is a major unmet need. AD is a common disease. The Public Health Agency of Canada estimated in 2017 that there were 402,000 Canadians living with dementia, and 76,000 new cases per year. AD is the most common cause of dementia. Addressing the unmet need for a disease modifying therapy for AD could improve the lives of hundreds of thousands of Canadians.

5. Place in Therapy

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

The approval of lecanemab would shift the current treatment paradigm. There are no current health Canada approved drugs that modify the course AD.

The mechanism of action of lecanemab is unique compared to other Health Canada approved treatments for AD. Lecanemab is a monoclonal antibody that binds to beta-amyloid, triggering the immune system to remove it from the brain. This is complementary to the mechanism of action of the cholinesterase inhibitors, which increased levels of the neurotransmitter acetylcholine, and memantine, which blocks NMDA receptors.

Lecanemab would be used as a complement to existing therapy with cholinesterase inhibitors. In the CLARITY-AD trial, most patients were concurrently taking cholinesterase inhibitors. Based on their very different mechanisms of action, there is no reason to believe that there would be drug interactions between lecanemab and the cholinesterase inhibitors.

Lecanemab has only been proven to be effective in patients in the early stages AD. In the CLARITY AD trial, participants were required to have a diagnosis of mild cognitive impairment or mild dementia due to AD, the presence of cerebral beta-amyloid based on a positive amyloid PET scan or lumbar puncture with CSF analysis, had a Folstein MiniMental Status exam score of 22 or higher, had a Clinical Dementia Rating Scale score of no higher than 1.0 (indicating no more than mild dementia), and had evidence of memory loss as shown on the Wechsler Memory Scale IV–Logical Memory II..

Prescribing lecanemab in clinical practice will require substantial changes in Canadian dementia systems of care. In the CCNA Preparedness for Alzheimer Disease Modifying Therapies In Canada Initiative, Working Groups will be reviewing these changes in order to synthesize current information and provide a Canadian agenda for research on adaptations in care paradigms, with plans for a full report to be released in fall 2024. Based on our current review of the literature, we anticipate that the most impactful changes to Canadian clinical practice will be:

- Testing to confirm the presence of brain beta-amyloid: Currently, the diagnosis of AD is based on the absence of other causes of dementia, informed by laboratory testing for non-AD conditions and usually a brain CT or MRI scan to exclude a mass lesion or vascular disease. Thus, AD is a clinical diagnosis made after excluding other conditions. To prove that beta-amyloid, the target for the drug, is present in the brain would require Canadian patients to have increased access to either amyloid PET imaging or lumbar puncture with CSF analysis of beta-amyloid and tau. Currently, these AD tests are only rarely used in clinical practice only rarely. There is limited capacity in Canada for amyloid PET testing, due to the small number of scanners and high expense. A research paper found that there would be higher capacity in Canada for CSF testing instead of PET (Black SE, et al. Can J Neurol Sci 2023:1-8); however, capacity for CSF testing is still probably less than what would be needed to test all Canadians who could potentially benefit from the drug. There is fast paced development of blood-based sensitive measures of amyloid and phospho-tau that are highly correlated to amyloid PET results. Their promise may help address this need by providing more accessible non-invasive testing alternatives (Hansson O, et al. Nat Aging 2023;3:506-519).
- Requirement for more frequent MRI scans: In the CLARITY AD trial, patients had 5 MRI over 18 months to monitor for radiological signs of ARIA, the most common complication of lecanemab therapy (van Dyck CH, et al. N Engl J Med 2023;388:9-21). ARIA can cause serious brain edema or hemorrhaging. In the US the prescribing information calls for similarly intensive MRI followup to identify this problem as patients may be asymptomatic or symptomatic with this complication and management depends on its identification. In current dementia practice in Canada, only one brain image (most commonly CT rather than MRI) is needed diagnostically to exclude conditions other than AD. The requirement for multiple MRIs may strain Canadian capacity for MRI scans, resulting in decreased access to lecanemab therapy or longer wait times for MRIs for other conditions.
- Requirement for drug infusion every 2 weeks: This will require access to a clinic or day medicine program for infusions, or arrangement for home intravenous infusion.

The requirement for access to beta-amyloid testing, MRI scans, and intravenous infusions will probably require treatment in specialized centers in larger urban areas; this has the potential to exacerbate geographic and other disparities in access to care in Canada.

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?

Lecanemab has only been proven to be effective in the early stages of AD. The view of our Steering Committee is that lecanemab is not appropriate for patients that do not meet the essential elements of the CLARITY-AD inclusion criteria: a diagnosis of mild cognitive impairment or mild dementia due to AD, Folstein MiniMental Status Exam score of 22 or higher, and evidence of beta-amyloid in the brain as shown by amyloid PET or lumbar puncture with CSF analysis. It would be helpful to provide specific prescribing information as, for example, is included in the US FDA package insert. Some of the assessments used to determine eligibility for CLARITY AD are not done in routine clinical practice in Canada, including the Clinical Dementia Rating and Wechsler Logical Memory test. A Working Group commissioned by the Steering Committee for the CCNA Initiative on Preparedness for Alzheimer Disease Modifying Therapies in Canada will examine criteria for eligibility in detail.

To be equitable, our view is that all patients in need of an intervention--which would be all patients with mild cognitive impairment or mild dementia due to AD--should be offered the opportunity to choose therapy if they meet eligibility criteria for treatment. A working group commissioned by the CCNA steering committee will review evidence for the number of potentially eligible patients across Canada, with separate estimates by province. A previous publication (Black SE, et al. Can J Neurol Sci 2023:1-8) estimated that less than 2% of patients in Canada had access to the resources required to receive AD disease modifying therapy similar to lecanemab. However, emerging evidence suggests that the denominator eligible population is smaller than previously believed. It is important to note that most patients with AD will not be eligible for this therapy, predominately because they have later stage disease. It is also the case that many patients with mild AD will have other contraindications treatment aside from the core criteria, such as need for

anticoagulation. Finally, we anticipate that some patients will choose not to receive therapy, given the requirement for frequent infusions and potential risks of side effects. It will be important to engage patients and their care partners in patient centred decision-making to help them decide whether this therapy is appropriate for them. The CCNA steering committee will commission a group on Clinical Effectiveness that will include persons with lived experience with dementia and their care partners to explore the patient and family focused considerations for whether to choose therapy or not. A report from this committee is expected in fall 2024.

AD is underdiagnosed in the community, particularly in the earliest stages proceeding dementia, such as when only mild cognitive impairment is present. To offer equitable treatment to all potentially eligible Canadians, improvements in systems of care for evaluating cognitive symptoms will be needed. This includes increased training for primary care providers in methods for evaluating patients with cognitive concerns. At minimum, this would include that primary care providers would need expertise in assessing cognitive function and cognitive related activities of daily living. The Montréal Cognitive Assessment (MoCA) is a cognitive assessment tool developed in Canada that can be administered in 10 to 15 minutes and is sensitive for detecting mild cognitive impairment or dementia. Increased access to specialists, including allied health professionals such as clinical neuropsychologists, will likely also be necessary. The complex decisions on eligibility and management of lecanemab will need to be taken by expert clinicians with considerable expertise in dementia care who are familiar with protocols for use of the drug.

Review of the effects of lecanemab in patient subgroups suggests that caution may be warranted in treatment of women and patients who carry two copies of the apolipoprotein E epsilon 4 allele (APOE4). According to supplemental figure S1 of the CLARITY AD main publication, women experienced 12% slowing of decline on the CDR-SB (main trial outcome) while men experienced 43% slowing of decline; the confidence intervals for these estimates were graphically displayed but not tabulated. The confidence intervals for women and men partially overlapped but an interaction p value was not shown. Furthermore, the confidence interval for women crossed zero. According to figure S3b, APOE4 homozygotes experienced -5% slowing of decline (i.e., they experienced a slight increase in symptoms over time); the confidence interval for AOE4 homozygotes overlapped the intervals for APOE4 heterozygotes and APOE4 noncarriers, and an interaction p value was not shown. A Working Group will comprehensively review information on effects and subgroups, with a plan to publish our results in fall 2024.

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?

In the CLARITY AD trial, the Clinical Dementia Rating Sum of the Boxes (CDR-SB) at 18 months was used as the primary endpoint. According to the main trial publication, “adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001)”. This is equivalent to a 27% reduction in the rate of decline in the lecanemab treated patients compared with placebo. Lecanemab successfully achieved its intended biological effect, with approximately two thirds of the treated group showing normalization of results of their amyloid PET scan.

However, there has been controversy over the clinical meaning of the 27% reduction in decline seen in the CLARITY-AD trial. The mean difference in CDR-SB at 18 months between lecanemab and placebo is less than the minimal clinically important difference derived in prior studies (Muir RT, et al. Alzheimers & Dementia 2024;20:3352-3363). However, those prior studies of the minimal clinically important difference did not actively engage patients with lived experience, the reliance on mean differences may obscure individually clinically meaningful responses in a subset of patients, and more meaningful differences could accrue over time if the rates of decline continued to diverge beyond 18 months. In the CLARITY AD trial, there was no indication that the treatment effects were reducing at 18 months, the end of the trial treatment period, but the treatment effects beyond 18 months are not known. The CCNA Steering Committee has commissioned a working group that includes persons with lived experience and their care partners to review the current state of the literature on the clinical importance of the different seen in the CLARITY AD trial, and to identify future research agenda. This will include evaluating other ways of expressing the treatment effects such as the “time saved” by slowing progression of AD (Dickson SP, et al. J Prev Alzheimers Dis 2023;10:595-599). A report from this group is expected in fall 2024. In

addition to needing a better, patient informed view of the clinical meaning of the effect of lecanemab, economic cost analysis studies are needed in the Canadian context to determine the value of lecanemab in relation to its cost. (However, please note that the actual conduct of such analyses is outside the scope of the CCNA Working Groups).

Based on the results of the CLARITY AD trial, lecanemab is expected to reduce cognitive symptoms from AD and improve daily function. In the CLARITY AD trial, these symptoms and functions were captured using the CDR-SB. However, the CDR is time consuming to administer (more than 60 minutes), is not routinely done in Canadian clinical practice, and is probably not feasible given the long administration time. We note that in the US Medicare registry for lecanemab treated patients shorter, more routinely used clinical tests can be used for patient monitoring, such as the Montréal Cognitive Assessment and Functional Activities Questionnaire (FAQ). This may be an appropriate approach for monitoring patients treated in Canada, as well. However, as discussed above, it is controversial whether the difference in rate of decline will be noticeable on an individual basis by patients or their clinicians. A Working Group commissioned by the CCNA will synthesize existing literature and offer suggestions for research on ways to monitor patients on lecanemab therapy. A report from this group is expected in fall 2024.

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

According to the CLARITY-AD trial, the main factors leading to discontinuation or interaction of treatment will be side effects of amyloid -related imaging abnormalities (ARIA) or infusion reactions.

ARIA are thought to result from excessive immune system reaction to treatment, leading to perivascular inflammation with resulting vasogenic edema, brain hemorrhage, or both. Symptoms of ARIA can include headache, delirium, seizure, focal neurological deficits, or hemorrhagic stroke. Serious complications can result, including hospitalization and death. In the CLARITY-AD trial, serious adverse events were reported in 126/898 patients on lecanemab and 101/897 patients on placebo. Deaths occurred in 6/898 on lecanemab and 7/897 patients on placebo. Symptomatic ARIA with edema occurred in 25/898 lecanemab and 0/897 placebo. Symptomatic ARIA with hemorrhage occurred in 6/898 lecanemab and 2/897 placebo. The CLARITY AD trial protocol included frequent MRI scans to screen for asymptomatic ARIA, which, when present, required modification of the lecanemab dosing protocol. In total, five MRI scans were required over an 18 month period including one end study MRI; however, in the presence of ARIA (which occurred in at least 17% of lecanemab treated patients) extra MRIs were required. The burden of doing multiple MRIs per patient adds to the system impacts of therapy (see our response to 5.1).

In the CLARITY AD trial, infusion reactions occurred in 237/898 on lecanemab and 101/897 on placebo. Infusion reactions may require treatment with antihistamines or, for more serious reactions, referral to an Emergency Department.

In the CLARITY AD trial, treatment was provided for 18 months. Whether the treatment-related effects persist beyond 18 months if treatment is discontinued, or whether lecanemab continues to be effective if administered continuously for more than 18 months, is not currently known. One possibility is that if clearance of beta-amyloid from the brain is achieved, then continued treatment beyond that point may not be necessary unless beta-amyloid re-accumulates. In the TRAILBLAZER ALZ2 study of donanemab, treatment with donanemab was discontinued when beta-amyloid removal was achieved. Whether this approach would be effective with lecanemab as well is not known. A working group commissioned by the CCNA rule review outstanding questions about duration of therapy with lecanemab and offer suggestions for future research agenda. Their report is anticipated in fall 2024.

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]?

Given the need for access to beta-amyloid testing, MRI scanning, and intravenous infusions, we anticipate that treatment would be provided more safely and effectively in specialized centres such as dementia specialty clinics. Monitoring for safety and freedom from ARIA requires MRI scanning with expert radiological interpretation, that is probably only available in larger care centres in urban areas. Due to the complexity of lecanemab therapy, it is probably most safely and effectively provided by specialists with expertise in dementia. This could include neurologists, geriatric psychiatrists, geriatricians, and family physicians with a practice focus on geriatrics or dementia.

However, to identify patients who should be offered treatment will require coordination with primary care providers, as dementia care in Canada is predominately centred in family practice. This will require more primary care providers to be skilled in assessment and diagnosis of mild cognitive impairment and dementia.

The Steering Committee for the CCNA Preparedness for Alzheimer Disease Modifying Therapies in Canada Initiative has commissioned working groups to synthesize existing information on provision of care and equitable access to care, with reports expected in fall 2024.

6. Additional Information

None.

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.

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

   No.

5. 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.

6. 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.**

   The CCNA is funded by a grant from the Canadian Institutes of Health Research,

Declaration for Clinician 1

Name: Eric Smith

Position: Professor of Neurology, Department of Clinical Neur

Date: 16-06-2024

☒ **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**
None				

Declaration for Clinician 2

Name: Howard Chertkow

Position: Professor of Medicine (Neurology), University of Toronto>

Date: 16-06-2024

☒ 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**
Eisai	x			
Biogen	x			

Eli Lilly	x			
Hoffman-La Roche Limited	x			

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

Declaration for Clinician 3

Name: Natalie Phillips, Ph.D.

Position: Professor of Psychology, Concordia University; Associate Scientific Director, CCNA

Date: 16-06-2024

☐ 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**
No conflicts of interest				

Declaration for Clinician 4

Name: Howard Feldman

Position: Professor, Department of Neurosciences; Director, Alzheimer’s Disease Cooperative Study at UC San Diego

Date: 16-06-2024

☒ 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**
Vivoryon Therapeutics				x
Novo Nordisk, Inc.		x		
Arrowhead Pharmaceuticals	x			
Roche/Genentech Pharmaceuticals	x			
Tau Consortium				x
Janssen Research & Development, LLC			x	
Association for Frontotemporal Degeneration (AFTD)	x			

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0822-000
Generic Drug Name (Brand Name): lecanemab (Leqembi)
Indication: Treatment of Alzheimer's disease (AD)
Name of Clinician Group: Clinique Interdisciplinaire de Mémoire du CHU de Québec
Author of Submission: Robert Laforce, MD, PhD

1. About Your Clinician Group

We are a group of physicians (3 Neurologists, 2 Geriatricians, and 1 NeuroPsychiatrist) practicing at the oldest Memory Clinic in Canada founded in 1967 by Dr Rémi W. Bouchard (see paper in Lancet Neurology, May 2017). We see patients with typical and atypical degenerative disorders in a multidisciplinary setting with nurses, OT, neuropsychologists, SLP and social workers. All of us combined, we see approximately 180 patients each week.

2. Information Gathering

Reading the original papers on monoclocal antibodies (aducanumab, lecanemab and donanemab) as well as editorials in our respective fields.

International meetings and local CME conferences where the use of Lecanemab and Aducanumab has been discussed by physicians experienced with these therapies.

Ad boards with Eisaï and Lilly on Lecanemab and Donanemab.

3. Current Treatments and Treatment Goals

The current drug treatment paradigm for AD in Canada is based on symptomatic treatments (ie, cholinesterase inhibitors and memantine) which only have a modest effect on cognition and behavior (see Cochrane Review, Birks 2009). Non drug treatments are mainly based on psychosocial and functional patient support and assistance to caregivers. Both of these treatments are supported by Canadian Clinical Practice Guidelines (see Ismail Z, Black SE, Camicioli R, Chertkow H, Herrmann N, Laforce R Jr, Montero-Odasso M, Rockwood K, Rosa-Neto P, Seitz D, Sivananthan S, Smith EE, Soucy JP, Vedel I, Gauthier S; CCCDTD5 participants. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimers Dement. 2020 Aug;16(8):1182-1195).

Current treatments do not address the underlying disease mechanism, which is believed to be related to accumulation of amyloid and tau pathology. Instead, they act as symptomatic treatments, which counterbalance the loss of acetylcholine, a neurotransmitter involved in attention and memory, associated with AD.

The most important goals that an ideal treatment would address are to delay disease progression, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers, prevent the need to move into a nursing home, and more generally reduced healthcare and social care costs of the disease.

It is noteworthy to mention that the Lecanemab study (van Dyck et al., NEJM 2022) met all of its primary and secondary outcomes, that is Lecanemab reduced markers of amyloid in early AD and resulted in moderately less decline on measures of cognition and

function than placebo at 18 months when all endpoints are considered. Similar results were found for Donanemab which led to approval by the FDA on July 3rd 2024.

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.

Current treatments (cholinesterase inhibitors and memantine) do not address the underlying disease mechanism which is believed to be related to accumulation of amyloid and tau pathology. Current treatments are not disease modifying drugs. Instead, they act as symptomatic treatments which counterbalance the loss of acetylcholine, a neurotransmitter involved in attention and memory, associated with AD. The three cholinesterase inhibitors are efficacious for mild to moderate AD (ie, improvements in cognitive function, on average -2.7 points). Despite the slight variations in the mode of action of the three cholinesterase inhibitors there is no evidence of any differences between them with respect to efficacy. The evidence from one large trial shows fewer adverse events associated with donepezil compared with rivastigmine (Cochrane Review, Birks 2009).

Current pharmacological treatments (cholinesterase inhibitors and memantine) are not indicated in the treatment of Alzheimer's disease at the mild cognitive impairment (MCI) stage.

The NNT (Number Needed to Treat) to observe global improvement for cholinesterases inhibitor is 12. The NNH (Number Needed to Harm) to observe discontinuation or cholinesterase inhibtors because of adverse eevents after 6 months is 15. (Data derived from Bond M et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): A systematic review and economic model. Health Technol Assess 2012;16(21):1-470. AND Guide d'Utilisation Optimale; Traitement pharmacologique, Maladie d'Alzheimer et démence mixte. Institut National d'Excellence en Santé et Services Sociaux, Mars 2015)

Current therapies for Alzheimer's Disease currently

Do not delay progression of disease; do not delay loss of cognition, loss of function in iADLs, ADLs, professionnal activities, leisure and hobbies, community affairs…

Do not address underlying pathophysiological mechanism of disease

Do not delay important milestones of disease (transition from 'MCI' to 'Dementia'; transition from mild dementia to moderate dementia…)

Do not delay other symptoms of disease: neuropsychiatric symptoms, behavioral symptoms…

Do not reduce or delay permanently caregiver burden

5. Place in Therapy

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

Yes Lecanemab would complement other available treatments by reducing the amount of amyloid in the brain. And it would be added to current pharmacological and non-pharmacological treatments. In clinical trials, subjects with early AD (defined as MCI due to Alzheimer's Disease and early Alzheimer's *dementia)* were recruited*;* so if Lecanemab becomes available in Canada it could be prescribed in some patients before cholinesterase inhibitors are even theorically recommended for them.

Lecanemab is one of the first treatments ever approved by the FDA to address the underlying disease process of AD and to slow the course of AD, rather than being a symptomatic management therapy.

Similar results were found for Donanemab which led to approval by the FDA on July 3rd 2024.

Lecanemab would be used as a first-line treatment, in combination with other pharmacological and non-pharmacological treatments.

The drug under review would not necessarily be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated – see criterias below.

Lecanemab has already caused a shift in the current treatment paradigm in the USA where it is approved, and is expected to impact Canada similarly.

It would not be appropriate to recommend that patients try other treatments before initiating treatment with Lecanemab since Lecanemab is the only disease-modifying treatment available while other treatments are only symptomatic treatments. There are no formal criteria to define what a treatment failure with the current treatments is. Moreover, time is of the essence in a degenerative disease such as AD so waiting for a trial with another non disease-modifying drug could jeopardize cognitive health in an irreversible manner.

Lecanemab would be the first treatment approved for the treatment of AD at the MCI stage.

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?

Patients with an amnestic MCI due to Alzheimer's Disease and/or early Alzheimer's dementia.

The patients described above are the most in need of an intervention.

This would differ based on disease characteristics (ie, this drug is only indicated in aMCI and mild AD).

Patients best suited for treatment with Lecanemab will be identified by clinician examination/judgement, cognitive tests, laboratory tests such as APOE4 dosing, and blood/CSF/imaging AD biomarkers.

Issues related to diagnosis include experience of the clinician with neurodegenerative disease and access to physicians.

Access to imaging techniques/centers (MRI, PETscans) could be an issue also, depending on provinces and regions (rural vs big cities) (Black, S.E. and al Can J Neurol Sci. 2023 Aug 18:1-8)

A companion diagnostic test is required in that proof has to be made of underlying AD pathology using either blood or CSF or imaging AD biomarkers.

Misdiagnosis does occur in clinical practice but here the requirements of an AD biomarker would reduce the likelihood that the drug would be administered to a non-AD patient. Still, there is a gap in the understanding of how positive biomarkers translate clinically. In other words, a patient with dementia caused by another disease than AD could be falsely diagnosed with clinical AD if the biomarkers are positive.

Since biomarkers can be positive BEFORE clinical symptoms of AD, and the drug is indicated for the treatment of early symptomatic AD, care should be taken before prescribing biomarkers; biomarkers should not be prescribed without a thorough clinical assessment and good evidence of early AD without confounding factors; counseling before and during for biomarkers results divulgation is a must to avoid catastrophic reactions from patients and caregiver

Identification of those patients who are most likely to exhibit a response to treatment with Lecanemab would be made by the clinician upon follow-up visits where cognition would remain relatively stable as well as daily activities.

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?

Outcomes used in clinical practice can be aligned with the outcomes typically used in clinical trials that is completion of cognitive tests and clinical dementia rating (CDR) yearly.

A clinically meaningful response to treatment would be a reduction in the expected rate of decline or a change in decline as observed by the patient and/or caregiver(s), in cognition and daily activities using repeated cognitive tests and CDR measurements (global score AND Sum of Boxes score). The magnitude of the response to treatment should be similar to those seen in the studies that is approximately in the range of 30% less decline over aprox. 18 months. The evaluations are possibly going to vary among clinicians depending on the experience of the physicians involved. Multiple trial-like assessments (scales, standardized questionnaires etc) will probably be necessary to capture slowing of decline, over many months.

Delay in crossing important clinical milestones (crossing from MCI due to AlzDisease to early AlzDementia for example) could also be important outcomes.

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

Treatment should be discontinued when the CDR has reached a score greater than 1 (major milestone).

Treatment should be suspended in case of symptomatic amyloid-related imaging abnormalities (ARIA); and discontinued in case of severe ARIA or repeated ARIA.

Trials, to date, have not evaluated starting Lecanemab in more severe AD patients than MCi due to AlzDisease and early AlzhDementia yet; efficacy in that subset is unknown, although previous studies with other anti-Amyloid therapy have done it without success. Follow up in the Lecanemab trials have been for 18 months, and subject were still in the MCI/early AD; continuation beyond the early AlzDementia stage hasn't been studied, nor has indication to stop beyond the early AlzDementia stage been properly set.

Given that the clinical effect of the treatment is expected to vary in time, the life expectancy and goals of care should be taken into account.

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]?

Community setting with specialized nurses, hospital (outpatient clinic) with specialized nurses and specialty clinic are all possible adequate settings.

A specialist is required for the initial determination of drug eligibility and follow-up of possible adverse events (brain edema and/or bleeding). The relevant specialties include Neurologists, Geriatricians and Psychiatrists (NeuroPsychiatrists).

GPs trained extensively in Cognitive disorders, Dementia and Alzheimer's Disease could probably select proper patients, and manage treatment, if supported by specialists/memory clinics for counseling if needed in special/atypical cases.

6. Additional Information

We recommend the following guidelines in accordance with AUC criteria by Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, Hendrix S, Selkoe D, Weiner M, Petersen RC, Salloway S. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377.

1. Have specific eligibility criteria (aMCI due to AlzDisease and/or mild AlzDementia, ≤3 microbleeds on MRI…)
2. Proper follow-up by specialized health care professionals (MDs specialists or well trained GPs, nurse paractitioners (planned MRIs and cognitive testing and CDRs)
3. APOE4 testing for identification of risk of bleeding and edema
4. Treatment discontinuation when CDR is >1 (until proven otherwise)

Dr Laforce from our clinic in Quebec City validated the DCQ (dcqtest.org); see Laforce et al., Arch Clin Neuropsychol. 2018; Sellami et al., Dement Geriatr Cogn Disord. 2018) which has a Memory Index /30 in both ENGLISH and FRENCH which we plan to use and instruct GPs to use for early detection of cognitive changes.

One must consider that Lecanemab was studied over only 18 months in a disease that spread over 20 years. Yet results showed that Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo. Long term studies will establish the impact of this drug over time.

Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6% and these need to be properly followed up in a structured format.

Similar results were found for Donanemab which led to approval by the FDA on July 3rd 2024.

7. Conflict of Interest Declarations

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

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

   No.

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

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <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.**

Robert Laforce: Eisai, Lilly
Louis Verret : Eisai; EliLilly; HoffmanLaRoche; Biogen; NovoNordisk
Yannick Nadeau : Eisai
Marie-Pierre-Fortin : Eisai
Pierre Molin : nothing to declare
Stéphane Poulin :

Declaration for Clinician 1

Name: Robert Laforce
Position: Neurologist, CIME du CHU de Québec
Date: 2024-05-05

☒ **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**
Eisaï	X			
Lilly	X			

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

Declaration for Clinician 2

Name: Yannick Nadeau
Position: Neurologist, CHU de Québec Université Laval
Date: <06-MAY-2024>

☒ 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**
Eisai	X			

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

Declaration for Clinician 3

Name: Marie-Pierre Fortin
Position: Geriatrician
Date: 15-05-2024

☒ 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**

Eisai	X			

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

Declaration for Clinician 4

Name: Louis Verret
Position: Neurologist, CHU de Québec Université Laval
Date: 04-06-2024

☒ 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**
Eisai	X			
EliLilly	X			
HoffmanLaRoche		X		
Biogen		X		
NovoNordisk	X			

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

Declaration for Clinician 5

Name: Pierre Molin
Position: geriatrician, CHU de Québec Université Laval
Date: 05-06-2024

I have no payments to declare.

☐ 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**

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

Declaration for Clinician 6

Name: Stéphane Poulin
Position: Psychiatrist CHU de Québec Université Laval
Date: 19-06-2024

I have no payments to declare.

☒ 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 6: Conflict of Interest Declaration for Clinician 6

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

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

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0822-00
Generic Drug Name (Brand Name): Lecanemab (Leqembi)
Indication: people with Mild Cognitive Impairment (MCI) or Mild dementia due to biomarker confirmed Alzheimer's disease (AD)
Name of Clinician Group: Consortium of Canadian Centres for Clinical Cognitive Research (C5R)
Author of Submission: Dr. Michael Borrie, Past President C5R and current executive member, with the executive members of C5R.

1. About Your Clinician Group

Organization Purpose and Website Link:

C5R is a not-for-profit research network that facilitates collaboration and partnerships between pharmaceutical companies and Canadian dementia researchers. C5R research sites conduct clinical trials in the desire to research developing treatments for patients with MCI, AD as well as other forms of dementia.

C5R - Consortium of Canadian Centres for Clinical Cognitive Research

2. Information Gathering

The information included in this submission is from

1. publicly available published scientific literature from the randomized controlled trial (RCT) with Lecanemab (NEJM Nov 29, 2022)

2. some of the Directors have participated in Advisory Boards to EISAI

3. the Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTDs). For over 30 years C5R members have contributed to the CCCDTDs and the resulting published clinical practice guidelines.

4. the current Directors of C5R have also drawn from their extensive clinical experience, particularly when commenting on section 3, Current Treatments and Treatment Goals, 4, Treatment Gaps, 5 Place and Therapy.

The first draft of the document was written by Dr. Borrie. Dr. Michael Borrie is a clinician researcher and site investigator, with the Cognitive Clinical Trials Group (CCTG), Parkwood Institute, London, Ontario. The CCTG conducts investigator initiated and pharma sponsored observational studies and RCTs in people with Mild Cognitive Impairment (MCI) and mild dementia due to Alzheimer's disease (AD). The draft was then read and edited by directors of the executive committee of C5R, who are also clinician researchers or clinician scientists in AD.

3. Current Treatments and Treatment Goals

Canadian Context

The Canadian context has been shaped by five CCCDTDs 1-5, 1989 -2019 and the resulting published clinical practice guidelines. See additional information section for references to the published guidelines.

Non-drug treatments for MCI and Mild dementia

Clinical recommendations and advice to patients and caregivers recommended by the CCCDTD guidelines

1. Regular aerobics/resistive weight exercise
2. Mediterranean style diet
3. Mental stimulation approaches
4. Socialization
5. Attention to restorative sleep practices/sleep hygiene
6. Alcohol or drug reduction/cessation

Drug treatments recommended by the CCCDTD guidelines

The Acetyl Cholinesterase Inhibitors (AChEI) are indicated for symptomatic treatment for people who have:

- mild to moderate dementia, clinically diagnosed as due to AD
- mixed Alzheimer's and vascular dementia or primary Lewy Body disease (LBD) or mixed AD and LBD
- They are not indicated for frontotemporal dementia.
- The three AChEI's are donepezil, rivastigmine and galantamine.

Memantine is indicated either

- as monotherapy
- combined with an AChEI for moderate/severe clinical AD
- clinical mixed dementia.

The AChEI and memantine are for symptomatic treatment only. They are not disease modifying in their mechanisms.

There are no treatments available through special access programs at this time.

Ideal Treatment Scenarios

An ideal treatment should target the mechanisms of AD when it is detectable using one or more recognized biomarkers of AD. These biomarkers include cerebrospinal fluid (CSF), positron emission tomography (PET), amyloid imaging and emerging blood biomarkers (p-tau181, p-tau217)

People with No Cognitive Impairment but at Risk

An ideal treatment would be effective to stop progression of the disease in asymptomatic people with biomarker confirmed AD.

People with Cognitive Impairment

An ideal treatment should stop the progression of clinical symptoms of asymptomatic biomarker proven AD and reverse any cognitive symptoms if they arise. An ideal treatment should stop progression of patient's symptoms of subjective cognitive decline (SCD) or symptoms of MCI in people who have biomarker proven AD as the underlying mechanism for their symptoms.

Slowing of Cognitive Impairment

A less than ideal treatment should slow progression of biomarker proven AD in people at risk without symptoms, or people with SCD or MCI or mild dementia due to AD.

Each of these ideal treatment scenarios with decreasing ability to stop, reverse, or slow the disease, would still reduce the severity of symptoms. They would increase the likelihood of maintained employment for longer, maintain independence in instrumental activities of daily living (IADLs) and self-care activities of daily living, reduce burden on caregiver and reduce the likelihood of the eventual need for long-term care

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 are no treatments approved in Canada at this time that stop, reverse or even slow the progression of AD.

The three AChEIs and memantine have modest effects.

From clinical experience, beyond the original 6-month RCTs for each of these compounds, about 40% of patients started on an AChEI alone or in combination with memantine, or memantine alone, have a positive response or stabilization of their progression of the disease, as evaluated by caregivers. This is not blinded information and potentially biased by positive expectations by caregivers.

Using clinical experience estimates, the side effects to the AChEI's, occur in about 10-15% of people and include, nausea, vomiting, diarrhea and urinary urgency leading to the discontinuation of the medication or the reduction in dose from the maximum recommended dose.

Using clinical experience estimates, the side effects to memantine, occur in 10-15% of people experiencing and include increased confusion, agitation, or constipation leading to the discontinuation or dose reduction from the maximum dose.

A symptomatic response, based on clinical experience can be anticipated for 6-12 months. Following these 6-12 months of improvement, or stabilization of symptoms, there usually will be progressive cognitive decline subjectively and objectively on cognitive tests.

Functional decline measured on Instrumental Activities of Daily Living (IADLs) scales occurs in a parallel manner to what might be expected for the natural course of AD.

There are no treatments at this time to stop, reverse or even slow the course of the disease.

Treatments are needed that will stop and potentially reverse the disease, or slow the disease particularly if it is detected when a person has no symptoms, meets the clinical criteria for SCD or the clinical criteria for MCI.

Adherence to the three AChEI's and memantine would be improved if they were less likely to cause side effects. The current formulations of the three AChEI's and memantine are relatively convenient, either being once a day or twice a day by mouth. Rivastigmine has been manufactured as a topical patch, and applied once a day may reduce side effects and improve adherence.

The provincial drug plan coverages of the above 4 medications are variable by province. For instance, in Ontario, memantine is not covered and costs about $4 per day. It's also not covered in BC and it's about the same price, $4/d or $120/month. The rivastigmine patch is also not covered and costs about $4.75/day, $143/month in ON and $6.20/day and $186 month in BC.

Limitations

The main limitation with the above treatments are the occurrence of side effects mentioned above with only modest symptomatic benefits. They do not alter the underlying pathological process.

5. Place in Therapy

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

Mechanism of Action

Lecanemab is a monoclonal antibody. It targets several species of amyloid in the blood and brain but in particular the neurotoxic oligomers. It also removes the protofibrils and fibrils already deposited in the brain. In the published RCT, the serial amyloid PET scans showed rapid clearance of amyloid from the brain and the p-tau181 plasma biomarker improved in a normalizing direction. The biomarkers analyses showed that Lecanemab modifies in a positive manner the biomarkers of AD.

With this confirmation of the mechanism of action Lecanemab will complement the other available treatments which are symptomatic treatment in their actions. If approved in by Health Canada, Lecanemab will be the first disease modifying treatment (DMT) in Canada.

Lecanemab is the first treatment to demonstrate slowing of the underlying disease process with robust clinical trial evidence.

The CCCDTD guidelines recommend the AChEI drugs be initiated in people with mild dementia but not be initiated in people with MCI.

Lecanemab will be the first treatment indicated for people with MCI due to biomarker proven AD and will be the first, first-line treatment for MCI due to AD.

Lecanemab will be indicated for people with MCI or mild dementia due to biomarker proven AD. It will be given to patients with MCI or mild dementia due to biomarker proven AD, regardless of whether or not patients were intolerant to an AChEI or whether AChEIs were contraindicated.

Lecanemab is expected to cause a shift in the current treatment paradigm. The approval of a disease-modifying therapy will highlight the incredible gaps in care that exist for early assessment and treatment of Alzheimer disease in Canada. Whereas other leading causes of death and disability such as stroke or cancer have well-organized provincial agencies and clinical care pathways, 12/13 Canadian provinces and territories do not have a dementia care pathway. The paradigm shift includes not only a drug that can modify the disease course, but facilitates the health care system to become better organized around dementia care.

Lecanemab treatment will not preclude treatment with AChEI. This is a therapy that can work in concert with the four existing symptomatic therapies.

Since there are no other drugs for symptomatic treatment or DMT for MCI due to biomarker proven AD, there is no other treatment to recommend before recommending Lecanemab for this patient population. For patients who have already progressed to mild dementia due to biomarker proven AD, there is no advantage to the patient to be recommended AChEI's before initiating Lecanemab since their AD pathological process will continue to progress. Lecanemab could slow the progression of their MCI and slow progression to moderate or to severe dementia.

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?

Based on the current Lecanemab RCT data - Most Likely to Respond:

Patients with MCI due to biomarker proven AD and secondly patients with mild dementia due to biomarker proven AD are most likely to respond to Lecanemab. With the current RCT evidence, these patients with MCI and mild dementia due to biomarker proven AD are the ones most in need of an intervention.

Stage of Disease

An ongoing trial of Lecanemab (AHEAD) in cognitively unimpaired people who are at risk of developing AD who have positive blood and amyloid PET scan biomarkers for accumulation of amyloid is still recruiting participants. The AHEAD RCT will determine whether beginning Lecanemab even earlier in people with beta amyloid pathology and no cognitive impairment, but who are at risk of AD, might benefit. The results of the AHEAD trial will not be known for another 2-4 years.

The most recent RCT evidence for Lecanemab (New England Journal November 29, 2022) did not inform whether Lecanemab would be a benefit to people who have moderate or severe dementia due to biomarker proven AD. It is generally considered that slowing of AD pathology in the moderate to severe stage is too late to make a clinically important difference.

In another study, Lecanemab is used in combination with a tau lowering therapy in the Dominant Inherited Alzheimer Network Treatment Unit (DIAN-TU-001) to access if it can slow the progression of disease in patients who carry the mutations causing young onset Alzheimer Disease in the presymptomatic, mildly symptomatic (MCI), and early symptomatic stages (mild AD), with results expected in 2027.

Issues Relating to Diagnosis

The clinical diagnosis of MCI or mild dementia needs to be made by a physician with expertise in the field of neurodegeneration/dementia.

Patients best suited for the treatment with Lecanemab need to be identified clinically first, as meeting the established clinical criteria for MCI or the established clinical criteria for mild dementia. Because of long waiting lists for qualified physicians, a triage system for rapid referral may need to be established.

Patients with MCI have a history of progressive cognitive decline, most commonly involving short-term memory.

Objective evidence of this progressive decline is confirmed by a common Canadian neurocognitive screening test called the Montreal Cognitive Assessment (MOCA). A score of less than 26/30 would be in the range for a diagnosis of MCI.

Repeated administration of the MOCAs or similar instruments can confirm objective evidence of improvement, stabilization or progressive decline.

Corroborated information obtained from a caregiver, indicating that a patients' cognitive impairment, compromising their independence for one or more of their known performance on IADLs, meets the criteria for dementia. Generally, it would be considered mild dementia if the standardized mini-mental state exam (MMSE) is 20/30 or higher.

A patient being considered as a possible patient to receive Lecanemab must have MRI-based neuroimaging. Specifically, a baseline MRI scan is necessary if Lecanemab is a treatment that a patient and their caregiver is considering with their physician who is knowledgeable and willing/able to prescribe Lecanemab therapy. The MRI with susceptibility weighted images (SWI) is to rule out the presence of significant silent brain haemorrhage (more than 4 microbleeds or evidence of macrohaemorrhage.)

A biomarker test used in the Lecanemab RCT, p-tau181 was an initial screening test. In the trial, if positive, it leads to CSF analysis or amyloid PET imaging. If either the CSF or PET imaging (whichever was more readily available and practical without contraindications ie. anticoagulants for lumbar puncture) was positive, the patient could be considered for inclusion in the trial.

Because of the risks for adverse events, initiation of treatment should be made by a physician with expertise in the field of neurodegeneration/dementia. The baseline MRI needs to be completed to rule out more than 4 microbleeds or macrobleeds.

The screening plasma biomarker (p-tau181) has been used in the Lecanemab clinical trial as a screening instrument. If positive, there is a high correlation that a person with a positive blood test will have a positive amyloid PET scan. For clinical trials, if the screening plasma p-tau181 or p-tau217 are negative, participants in the clinical trials did not proceed to having an amyloid PET scan.

Amyloid PET scans are expensive and have not been clinically available in most provinces. Hopefully blood biomarkers for beta amyloid 42 will become recognized and accepted as a proxy for Amyloid PET scanning or Lumbar puncture. (i.e. preclivity, not yet approved in Canada)

CSF is likely to become more clinically available. It is dependent on specialists who have the expertise to do a lumbar puncture (LP) to obtain the CSF for analysis. More specialists are being trained to perform LPs. A national reference lab for the analysis of CSF biomarker is available in Vancouver.

The future approval of and clinical availability of one or more blood biomarkers for AD might reduce the future need for expensive PET amyloid scans and time-consuming lumbar punctures. Until such an approval of one or more blood biomarkers and clinical availability is widely available, determination of AD pathology at baseline will be dependent on amyloid PET scans or CSF analysis.

Companion Diagnostic Tests

The companion diagnostic tests required highlight as above – MRI, brain using SWI sequences to rule out more than 4 microbleeds, and/or macrobleeds, plasma p-tau181 or p-tau217 as a screening test to inform whether to proceed to amyloid PET scan or lumbar puncture with CSF analysis. Plasma, p-tau217 has been shown to be more sensitive and specific than p-tau181 used in the Lecanemab RCT. MRI must also be available to monitor potential side effects of ARIA in the first 6 months of treatment.

Genetic testing for ApoE status has been recommended. Patients with the E4 allele of the ApoE gene are at higher risk of ARIA and are also at higher risk of progression to dementia if diagnosed with AD pathology. ApoE genetic status will need to be accounted for to tailor patient discussions about benefits and risks of lecanemab therapy. ApoE testing is available in Canada.

Under Diagnosis

Cognitive impairment in older individuals is generally underdiagnosed. It is unrecognized or not acknowledged by the person who may have lack of insight to their impairment.

There is a stigma against AD. Caregivers may dismiss the onset of short-term memory impairment as being “just due to old age”.

Some family physicians are uncomfortable doing the clinical assessments and screening neurocognitive tests such as the MOCA. The assessment is time consuming and not easily accommodated, in family physician’s short appointment times.

A diagnosis requires additional input, quite separately, from a knowledgeable partner/spouse, daughter or son, or other family member or friend who knows the person well.

Preliminary data from the Lecanemab RCT, exploring subgroups who may be more responsive has not been published as of April2024.

There are ongoing subgroup analyses from the RCT to determine whether some subgroups are more likely to exhibit a response than others.

There is also a lack of evidence on patients outside of the clinical trial criteria. For instance, patients with young onset dementia under the age of 60 (which was the cutoff for the inclusion criteria for the published trial). There is no data on atypical presentation of Alzheimer disease, such as logopenic progressive aphasia, or posterior cortical atrophy, which often have underlying Alzheimer pathology. Specific studies tailored to these populations will be needed to guide application of disease modifying therapy.

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?

Outcome Measures

The outcome measures used in clinical practice are usually briefer, less in-depth assessments, than those used in RCTs particularly as it applies to measures of cognition. In Canadian clinical practice the MOCA is the most common cognitive outcome measure used in primary care and specialist practices, such as Memory Clinics.

The total score on repeated MOCA over months and years can be followed between primary care and specialist memory clinics to confirm cognitive improvement, stability or decline. The MOCA correlates with the more in-depth instruments used in clinical trials.

There are various clinical functional measures, including the Lawton-Brody Instrumental Activities of Daily Living Scale, the Disability Assessment for Dementia (DAD) (. The ADCS MCI-ADL scale is often used in clinical trials and could be also used in clinical practice to measure functional change over time with repeated measurements. However, the administration of this scale is cumbersome and time-consuming and may not be practical in everyday clinical practice. A simplified scale that assesses daily function will be very useful in monitoring patients on treatment.

Clinically Meaningful Response Findings

Clinically meaningful responses based on the RCT would include, slowing of cognitive decline, slowing of functional decline and maintenance of independence in IADLs over time.

There will be some variability between physicians as to what they consider a clinically meaningful response. However, when considering an individual patient, there is no comparator to know what that person's natural progression of AD might have been in the absence of treatment.

If the physician (family physician or specialist) following a person over time, using repeated questionnaires or other objective measures, they may be able to determine a plotted slope of decline on these scales. Continued, repeated measures after initiation of treatment, might show a shallower trajectory of decline on the cognitive scale(s) and IADL scale(s) suggesting slower decline or stabilization of decline.

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

Discontinuation/Endpoints

From the Lecanemab RCT, clearance of amyloid on repeat amyloid PET scan was confirmed. However, for clinical practice this is not practical because the cost and lack of availability of amyloid PET scans. Progression from MCI or mild dementia due to biomarker proven AD to moderate or severe dementia could be another endpoint. Progression of disease with increasing dependence in IADLs and later dependence in self-care ADLs could be a further treatment endpoint. Admission to long-term care facility could be an endpoint.

A clinical endpoint-based termination criterion, or a time-based criterion could be a practical solution.

Treatment Pause/Discontinuation

Adverse events such as symptomatic Amyloid Related Imaging Abnormality – edema (ARIA-E) or symptomatic Amyloid Related Imaging Abnormality-hemorrhage (ARIA-H) are detected on urgent MRI done at the time of onset of symptoms. ARIA-E and ARIA-H while on treatment, would be a reason to pause treatment until the symptoms have resolved and repeat MRI have confirmed radiographic resolution of ARIA-E and ARIA-H. This was the study protocol within the clinical trial and other RCTs with other similar compounds. ARIA-E and ARIA-H are more likely to occur within the first 6-months of initiation of treatment and less likely to occur after one year on treatment.

Objective confirmation of ARIA-E and ARIA-H is by MRI scan done urgently at the time of the onset of symptoms. New microbleeds while on treatment and particularly macrobleeds could be additional reasons for discontinuing treatment depending on the published Lecanemab: Appropriate Use Guidelines. Cummings et al.

5.5 What settings are appropriate for treatment with lecanemab? Is a specialist required to diagnose, treat, and monitor patients who might receive lecanemab ?

Specialists required

Specialists are required for assessing patient's suitability for Lecanemab therapy. They include neurologists, geriatricians, geriatric psychiatrists who have a special interest, training and experience in making the clinical diagnosis of MCI and mild dementia and who have training in the interpretation of the screening blood biomarkers (p-tau181/p-tau217, CSF interpretation and amyloid PET interpretation, and have the knowledge to appropriately manage people experiencing side effects of ARIA

Initially confirmation of diagnosis by a specialist experienced with the interpretation of appropriate amyloid biomarkers is important. Family physicians working in dementia assessment clinics who have acquired added competency in management of dementia could be included.

The Lecanemab RCT required 5 additional MRI's for safety over 18 months, particularly monitoring of ARIA. Centres giving Lecanemab must be able to provide this reliably.

Radiologists trained in identifying microbleeds on the baseline MRI susceptibility weighted images are necessary before proceeding to treatment. Neuroradiologists and community radiologists trained and educated in recognizing ARIA-E and ARIA-H are necessary as part of the team managing patients initiated on Lecanemab. Trained neurologists, geriatricians, geriatric psychiatrists, anesthetists and possibly nurse practitioners able to perform LP for CSF collection in an outpatient setting need to be available, particularly when PET imaging in not available.

Where PET imaging is available, nuclear medicine physicians will need to be trained in the interpretation of amyloid PET scans as to whether amyloid PET scans meet the threshold for being positive or negative on the centiloid scale or equivalent scale.

Radiologists, educated on and able to quickly interpret baseline MRI scan susceptibility weighted images for microbleeds and subsequent urgent MRI scans for patients on treatment who develop new neurologic symptoms which might be due to ARIA-E or ARIA-H need to be available.

Laboratory Medicine specialists or Clinical Chemists may also be needed to supervise and interpret findings from CSF measurements of biomarkers (Amyloid Beta 42, total tau, p-tau181 or p-tau 271, etc).

Infusion Centres

Lecanemab is administered intravenously every 2-weeks. From the RCT it was for a period of 76 weeks.

Infusion centres need to be available either in the hospital or outpatient setting with nursing staff educated to observe for local infusion reactions or systemic reaction, particularly with or after the first few infusions.

There will need to be linkages between the specialist diagnosing people with MCI or mild AD due to biomarker proven AD and a prescribing specialist if not the same as the diagnosing specialist. The trained radiologist for the baseline MRI and the infusion centre should be linked if there are any adverse reactions with the infusion. As well, the patient's primary care physician, and prescribing physician need to be linked in if there are any new neurologic symptoms after or between infusions.

Additionally, prescribing physicians must have some mechanism for after-hours care. For example, if part of a call group, then members of the call group will need to be aware of Lecanemab and ARIA E and ARIA-H.

6. Additional Information

Lecanemab - N Engl J Med 2023; 388:9-21 DOI: 10.1056/NEJMoa2212948

Cummings et al. Lecanemab: Appropriate Use Recommendations J Prev Alz Dis 2023

CCCDTD4 *Canadian geriatrics journal: CGJ* vol. 15,4 (2012): 120-6. doi:10.5770/cgj.15.49

CCCDTD5 - Alzheimers Dement. 2020;16(8):1182-1195. doi:10.1002/alz.12105

MOCA - mocacognition.com

Disability Assessment in Dementia; Gelinas et al, Am J Occup Ther 1999

7. Conflict of Interest Declarations

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

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

   No

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

   Mr. William Jagger, C5R in collaboration with Dr. Michael Borrie assisted to collate the responses from the executive committee members of C5R.

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.**

   C5R has received financial payments over the last 2-years from the following pharmaceutical companies for completing scientific reviews of study protocols

   Facilitating connections between potential C5R clinical trial site and pharmaceutical companies.

   Supporting recruitment of participants to clinical trials.
   Supporting regular telephone calls with participating C5R site in a trial for recruitment and retention of participants
   Clinical trials funding to conduct clinical trials, under contract, are paid to affiliated research organizations and managed to support the clinical trials research team at the research site.
   Immediate from pharma companies.

Sponsor	Protocol
AbbVie	M22-721 (HARBOR)
Acumen Pharmaceuticals	ACU193-201 (ALTITUDE-AD)
Alector	AL002-02
Alector	AL002-LTE
Alzheon Inc	ALZ-801-AD301 (APOLLOE4)

Alzheon Inc	ALZ-801-AD351 (APOLLOE4-LTE)
Anavex	2-73-AD-004
Anavex	2-73-AD-EP-004
Otsuka Pharmaceuticals Inc.	20-AVP-786-307 (ASPECT)
Biogen	221AD305 (ENVISION)
Biogen	221AD304 (EMBARK)
Biogen	247AD201 (CELIA)
Cerevel	CVL-871-2001
Eisai Inc	BAN2401-G000-201
Eli Lilly	15T-MC-AACH (TRAILBLAZER EXT)
Eli Lilly	15T-MC-AACI (TRAILBLAZER-ALZ 2)
Eli Lilly	I9X-MC-MTAE
Eli Lilly	J1G-MC-LAKD (TRAILRUNNER-ALZ 2)
Eli Lilly	J1G-MC-LAKF (TRAILRUNNER-ALZ 3)
GlaxoSmithKline Inc.	219867 (PROGRESS-AD)
Greenvalley	GV971-007 (GREEN MEMORY)
Hoffmann-La Roche Limited	BP44745 (GABriella)
Hoffmann-La Roche Limited	WN41874 (OpenRoad OLE)
Hoffmann-La Roche Limited	WN42171 (POSTGRADUATE)
Hoffmann-La Roche Limited	WN42444 (Skyline)
IGC Pharma LLC	IGC-AD1-P2 BIDAG
IntelGenx	IGX-CLI-2017-001 (BUENA)
Janssen	63733657ALZ2002 (AUTOMONY)
Novo Nordisk, Canada Inc.	NN6535-4725 (EVOKE Plus)
Novo Nordisk, Canada Inc.	NN6535-4730 (EVOKE)
Cassava	PTI-125-06 (REFOCUS-ALZ)
Cassava	PTI-125-10 (OLE)
WAVE Life Sciences UK Limited	WVE-004-001

Declaration for Clinician 1

Name: Dr. Michael Borrie
Position: Past president and current Director, C5R
Date: 28-02-2024

☒ **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**
Eisai (as a consultant)			X	
EISAI (paid to the institution as a clinical trials site investigator)				X
Eli Lilly (as a consultant		X		
Biogen (as a consultant)		X		
Biogen (paid to the institution as a clinical trials site investigator)				X
Roche		X		
Janssen (paid to the institution as a clinical trials site investigator)				X
Alector (paid to the institution as a clinical trials site investigator)				X

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

Clinical Trials funding, from pharma companies to conduct clinical trials under contract with the Cognitive Clinicial Trials Group at Parkwood Institite' is paid to the Lawson Health Research Institute.

Declaration for Clinician 2

Name: Ging-Yuek Robin Hsuing
Position: President, C5R
Date: 08-03-2024

☒ 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
Eisai (as a consultant)		X		
Eli Lilly (as a consultant)		X		
Roche (as a consultant)	X			
NovoNordisk (as a consultant)	X			
Cassava (to the institution only)				X
Biogen (to the institution only)				X
NIA / DHHS (grant on study Asian Cohort on Alzheimer Disease AD)				X

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

Declaration for Clinician 3

Name: Andrew Frank
Position: Secretary/Treasurer
Date: Mar 5, 2024

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

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Lilly Canada		X		
Eisai Canada		X		
Roche Canada	X			
Novo Nordisk	X			

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

Declaration for Clinician 4

Name: Stephen Pasternak
Position: Chair, Protocol Review
Date: 15-03-2024

☒ 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**
Eli Lilly (Consultant)	X			
Cassava (to the institution as a clinical trials site investigator)			X	
Zywie Bio LLC (to the institution as a clinical trials site investigator)				X

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

Declaration for Clinician 5

Name: John Marotta
Position: Member Finance Committee, Protocol Assessment and Review Committee
Date: 12-03-2024

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

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eli Lilly (as a consultant)		X		
Biogen (clinical trials paid to institution only)			X	
Cassava (clinical trials paid to institution only)			x	
Optina Diagnostics clinical trials paid to institution only)			x	

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

Declaration for Clinician 5

Name: Alex Henri-Bhargava
Position: Director at Large
Date: 07-03-2024

☒ 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**
Eisai (Consulting)		X		
Eli Lilly (Consulting)	X			
Roche (Consulting)	X			
NovoNordisk (Clinical trial funding)*				X*
Canadian Coalition for Seniors' Mental Health (Clinical Guidelines Development)	X			
Intelgenx (Clinical trial funding)*				X*
Cerevel (Clinical trial funding)*				X*
Anavex (Clinical trial funding)*				X*
Green Valley Shanghai (Clinical trial funding)*				X*
Canadian Consortium on Neurodegeneration in Aging				X*
Centre on Aging and Brain Health Innovation (Research grant)			X*	

* Clinical trials funding from pharmaceutical companies and non-governmental agencies to conduct clinical trials and research under contract with the Clinical Trials Unit at the Royal Jubilee Hospital is paid to the Vancouver Island Health Authority. Compensation for Dr. Henri-Bhargava's involvement is paid to him by the Health Authority and not directly by funders.

CADTH Project Number: < SR0822-000 >
Generic Drug Name (Brand Name): < lecanemab (Leqembi)>
Indication: <Mild Cognitive Impairment due to Alzheimer's disease and mild Alzheimer's disease>
Name of Clinician Group: <Geriatricians at Trillium Health Partners>
Author of Submission: <Drs. Shiv Khosla, Jason Kerr, Amina Jabbar, Ahmad von Schlegell>

1. About Your Clinician Group

We are part of a group of 14 community-based geriatricians in Mississauga, Ontario with academic appointments at a large academic centre. We practice inpatient and outpatient geriatrics with a large portion of our clinical visits being for dementia and it's complications.

2. Information Gathering

Information was gathered through a literature review including the following:

- Amyloidosis in Alzheimer's Disease: Pathogeny, Etiology, and Related Therapeutic Directions - PMC (nih.gov)
- Long-Term Health Outcomes of Lecanemab in Patients with Early Alzheimer's Disease Using Simulation Modeling - PMC (nih.gov)
- Biogen to Realign Resources for Alzheimer's Disease Franchise | Biogen
- Expected and diagnosed rates of mild cognitive impairment and dementia in the U.S. Medicare population: observational analysis - PMC (nih.gov)
- Psychosis linked to higher misdiagnosis rates in dementia patients, study suggests - Unity Health Toronto
- Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants | Alzheimer's Research & Therapy | Full Text (biomedcentral.com)
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3487532/
- https://www.nejm.org/doi/suppl/10.1056/NEJMoa2212948/suppl_file/nejmoa2212948_protocol.pdf
- https://link.springer.com/article/10.1186/1471-2377-14-101

3. Current Treatments and Treatment Goals

Currently, in Canada, dementia is a terminal diagnosis. The most common cause of dementia, Alzheimer's disease, is slowly and gradually progressive over an average of 8-12 years from symptom onset to death. Medications for Alzheimer's that are currently in circulation are cholinesterase inhibitors (donepezil, galantamine and rivastigmine) for mild, moderate and severe disease, and a N-methyl-D-aspartate (NMDA) receptor antagonist (memantine) for severe dementia. The classes of medications can either be used independently or combined. These medications have a modest effect in treating some symptoms of Alzheimer's disease but do little to slow the progression and nothing to modify the underlying mechanism.

The costs of cholinesterase inhibitors are covered by the Ontario Drug Benefit up to a certain point in the disease trajectory - until the Mini Mental Status Examination (MMSE) score falls below 10. Memantine is not covered and can cost patients between $100-130 per month depending on which pharmacy they use.

Ultimately, in the current state, patients with dementia decline and ultimately need assistance from caregivers for their basic activities of daily living, which include bathing, dressing, grooming, feeding, toileting and transferring. Caregivers are either family members, friends or community members, PSWs from Homecare and Community Support Services (HCCSS) or hired privately. Caregivers shoulder a significant burden of care, which lead to economic costs with a decrease in work hours and/or inability to work, inability to look after their own families, and worsening of their own

medical conditions such as depression, anxiety and stress related diseases such as hypertension among many other diseases.

Lecanemab differs from currently available treatments in that it is a monoclonal antibody that significantly decreases the number of amyloid deposits in the brain. This is important as the amyloid hypothesis suggests that deposition of beta-amyloid in the brain leads to toxicities causing Alzheimer's disease. Decreasing the amyloid in the brain is theorized to modify the underlying disease mechanism, thus delaying the progression of the disease leading to prolonging life, delaying functional decline, improving health-related quality of life, maintaining independence and decreasing caregiver burden. Delaying disease progression is also theorized to delay the need for admission to long-term care.

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.

Cholinesterase inhibitors and memantine are currently widely available treatments for people with Alzheimer's dementia. These medications do not modify the underlying pathology of the disease. Thus, a patient with Alzheimer's dementia will progress to functional dependency whether they take these medications or not. Newer treatments that sustainably modify the way that Alzheimer's dementia progresses are needed to maintain functional independence, improve quality of life and decrease caregiver stress.

No medications are currently approved for Mild Cognitive Impairment (MCI) due to Alzheimer's disease. Literature suggests that earlier interventions in progressive cognitive decline lead to a slower disease trajectory, projecting a slower loss of function.

5. Place in Therapy

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

If approved, Lecanemab will be the first medication in Canada that would be disease modifying by reducing the amount of amyloid in the brain. It would be used first line in patients with MCI due to Alzheimer's disease and mild Alzheimer's disease. In the Clarity-AD trial, Lecanemab was given to patients who were taking a cholinesterase inhibitor, memantine, or both. Data showing differences in response to patients taking a currently available medication with and without Lecanemab is not available. Lecenameb has the potential to cause a shift in the current treatment paradigm of dementia patients. If approved, it can delay the progression from MCI due to Alzheimer's disease to dementia, and delay the rate that dementia progresses by roughly 31% in the Clarity AD trial.

It would not be appropriate for patients to try currently available treatments prior to treatment with Lecanemab, as the disease will continue to progress in severity leading to worsening cognition and function for the patient. Delaying treatment with Lecanemab will allow the disease to progress past the mild stages, making them ineligible for treatment per the clinical use criteria that have been made. Lecanamab should be given earlier in the course of the disease to attempt to further prevent the decline associated with Alzheimer's dementia.

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?

The patients who would be best suited for treatment with Lecanemab would reflect the patient population in the Clarity-AD trial. These include MCI due to Alzheimer's disease and mild Alzheimer's disease. People with MCI due to other causes, Alzheimer's disease with a severity greater than mild, or a diagnosis of other forms of dementia would not be eligible for Lecanemab at this time based on the evidence available.

Eligible patients would be identified from the referral pool to specialists including geriatricians, neurologists, geriatric psychiatrics, and memory clinics. The encounter would involve a detailed cognitive history, with focus on cognitive domains, a functional inquiry, ruling out other potentially contributing factors, cognitive testing and a physical exam. The cognitive domains are memory and learning, speech and language, executive function, motor perception, complex attention, social attention, and motor functions. The functional inquiry includes a review of basic and instrumental activities of daily living. On history, potentially reversible causes of cognitive decline such as a stroke, depression, anxiety, other neurological conditions such as Parkinson's disease, and head trauma are ruled out. Cognitive testing may include the Standardized Mini Mental Status Examination (MMSE) with published use criteria of 22-30,

In addition to routine guideline-based screening to rule out potentially reversible causes of dementia, the presence of amyloid must be proven. For Lecanemab, this can be completed with either an amyloid PET scan of the brain or p-tau/AB42 cerebrospinal fluid (CSF) biomarkers. In the current state, in Mississauga, amyloid PET scans are only available for research purposes, not for assisting with dementia diagnosis. CSF biomarkers are not available in the public payor system.

There are several issues related to diagnosis. In the current state, mild cognitive impairment (MCI) is under-diagnosed. Potential reasons for under-diagnosis include patients and families feeling that the cognitive changes they are experiencing are normal due to aging, front-line primary care physicians not being aware of the difference between normal aging and MCI, and patients not having access to a family doctor or specialist in memory care. This under-diagnosis is more prevalent in the non-white population.

Misdiagnosis of MCI due to Alzheimer's disease and Alzheimer's dementia does occur in clinical practice as there are many symptoms, particularly hallucinations and delusions, that overlap with other forms of dementia, for example, lewy body dementia and Parkinson's disease dementia. The introduction and utilization of biomarkers to the standard of care for diagnosis of Alzheimer's disease will allow for an earlier, more accurate diagnosis for patients, and allow for personalized treatment to be tailored to their disease subtype.

Based on current data available, it is not possible to predict which patients with MCI due to Alzheimer's disease and mild Alzheimer's disease will exhibit a response to Lecanemab.

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?

Outcomes used in clinical practice include cognitive tests such as the Montreal Cognitive Assessment (MOCA) and Standardized Mini Mental Status Examination (MMSE). Given the progressive nature of the disease with current unavailability of disease modifying medications, it is anticipated that all patients with dementia, whether they are on treatment or not, will have a gradual decline in their cognitive scores. Given that all patients progress at a different rate, and their baseline scores are heterogenous, and as a practitioner in the office setting, we cannot compare one person's baseline score and rate of decline to another. Introduction of a disease modifying medication could result in a meaningful slowing of the decline in cognitive testing scores. Literature suggests that over a longer duration of therapy, there may be larger differences in the rates of cognitive and functional decline.

Another way progression is assessed is through a detailed history from the patient with dementia and someone who can provide accurate collateral history. Through this, a reliable functional history can be obtained, and the disease trajectory can be followed on the Global Deterioration Scale. The trajectory of a patient on treatment can be compared to current anticipated norms.

Using standardized cognitive tests and the Global Deterioration Scale ensures homogeneity in the assessment regardless of the assessor.

In research, scales commonly used include the ADAS-Cog and the Clinical Dementia Rating Scale, which can take 40 and 90 minutes to administer respectively. This is not practical for use in day-to-day practice.

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

When to stop Lecanemab in the trajectory of dementia has not been adequately studied. Ongoing investigation into recommended dose and frequency of Lecanemab after the initial biweekly infusion for 18-months is currently ongoing. There are no current guidelines dictating that Lecanamab should be discontinued if Alzheimer's progresses past the mild stage.

In the recently published Lecenamb appropriate use recommendations which was published in J Prev Alz Dis 2023;3(10):362-377, most centers are following protocols developed based on these recommendations.

In the Clarity-AD study, participants were discontinued from the study if:

- "Resumption of treatment following the occurrence of ARIA-H of symptomatic cerebral microhemorrhages, symptomatic superficial siderosis, or any macrohemorrhage can only occur twice, after which the subject must be discontinued from the study drug."
- "For subjects who already have ARIA-H of >10 cerebral microhemorrhages, should further new microhemorrhages develop after resumption of treatment, the subject must be discontinued from the study drug."
- "Resumption of treatment following symptomatic and/or radiographically moderate or severe ARIA-E can only occur twice, after which the subject must be discontinued from the study"
- "If severe ARIA-E is associated with SAE (results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in persistent or significant disability) the drug will be permanently stopped and no re-challenge can be considered."
- "hypersensitivity reactions with clinical features of tissue injury (eg, arthritis, glomerulonephritis, mononeuritis multiplex) will be immediately discontinued from study drug"
- "Infusion reactions associated with administration of study drug, of Grade 3 severity or above as defined in the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), that do not lessen or resolve with treatment"
- "Clinical features which indicate meningoencephalitis (eg, combination of 1 or more of the following: headache, worsening confusion, neck stiffness, impaired consciousness, focal neurological signs)"

Other reasons to consider discontinuation of Lecanemab:

- Patient and/or substitute decision maker desire to discontinue the study drug
- Development of any of the exclusion criteria used in the study, which include:
    - Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment, or any non-AD MCI or dementia
    - MRI findings of:
        - More than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter)
        - a single macrohemorrhage >10 mm at greatest diameter
        - an area of superficial siderosis; evidence of vasogenic edema
        - more than 2 lacunar infarcts or stroke involving a major vascular territory
        - severe subcortical hyperintensities
        - CAA
        - amyloid beta-related angiitis
        - Other major intracranial pathology that may cause cognitive impairment
        - MRI evidence of non-AD dementia
    - History of TIA, CVA or seizures within 12 months of screening

- Mental health – psychosis, GDS >8
- Uncontrolled immunologic disease, or disease that requires treatment with immunosuppressants, immunoglobulins, monoclonal antibodies
- Uncontrolled bleeding disorder, including plt < 50 and/or INR > 1.5
- Patients on anticoagulation (tPA should not be administered)
- Unstable medical conditions

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]?

Lecanemab can be administered in a hospital setting, infusion center or specialty care clinic that has first-aid capabilities and is well equipped to treat transfusion reactions. Specialists, including Geriatricians and Neurologists are required to diagnose, treat and monitor patients who might receive Lecanemab.

6. Additional Information

<Enter Response Here>

7. Conflict of Interest Declarations

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

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.
   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.
   No.

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

Declaration for Clinician 1

Name: Shiv Khosla
Position: Geriatric Physician
Date: 10/06/2024

X **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**
Add company name				
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 2

Name: Jason Kerr
Position: Geriatric Medicine Specialist
Date: 12/06/2024

X 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**
Add company name				
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 3

Name: Dr. Amina Jabbar
Position: Geriatric Medicine Specialist <Enter currently held position>
Date: 13-06-2024

X 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**
Add company name				
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 4

Name: <Ahmad von Schlegell >
Position: <Geriatric Medicine Specialist>
Date: <13-06-2024>

X 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**
Add company name				
Add company name				
Add or remove rows as required				

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