

## Reimbursement Recommendation

# Lecanemab (Leqembi)

**Indication:** For the treatment of adult patients with a clinical diagnosis of mild cognitive impairment or mild dementia due to Alzheimer's disease (early Alzheimer's disease), who are apolipoprotein E epsilon 4 (ApoE epsilon 4) noncarriers or heterozygotes, and who have confirmed amyloid pathology

**Sponsor:** Eisai Canada

**Final Recommendation:** Reimburse with conditions

# Summary

## What Is the Reimbursement Recommendation for Leqembi?

Canada's Drug Agency (CDA-AMC) recommends that Leqembi be reimbursed by public drug plans for the treatment of adult patients in the early stages of Alzheimer disease (AD) (i.e., mild cognitive impairment [MCI] or mild dementia) who have evidence of amyloid in the brain and who are *APOE* epsilon 4 (*APOE*4) noncarriers or heterozygotes, if certain conditions are met.

## Which Patients Are Eligible for Coverage?

Leqembi should only be covered to treat adult patients aged 50 years or older who have a clinical diagnosis of early AD with confirmed amyloid pathology using a validated method, and who are *APOE*4 noncarriers or heterozygotes.

## What Are the Conditions for Reimbursement?

Leqembi should only be reimbursed if prescribed by clinicians with expertise and experience in the diagnosis, management, and treatment of AD, in a setting with timely access to MRI. Treatment should not be initiated, and should be discontinued, in patients who are unable or unwilling to undergo the recommended MRI monitoring for amyloid-related imaging abnormalities (ARIAs). Leqembi should only be used in patients without symptomatic ARIAs or moderate to severe radiographic ARIAs, and if the cost of Leqembi is reduced. Leqembi should not be reimbursed in combination with other monoclonal antibody therapies for AD or upon disease progression to moderate dementia.

## Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Leqembi is likely to provide a meaningful benefit in reducing cognitive and functional decline to a degree that may address a substantial unmet clinical need for patients with early AD and their caregivers.
- Based on the CDA-AMC assessment of the health economic evidence, Leqembi does not represent good value to the health care systems at the public list price. A price reduction is therefore required.
- Based on public list prices, Leqembi is estimated to cost the public drug plans approximately \$728 million over the next 3 years. However, the actual budget impact is uncertain and will depend on the number of patients who are eligible for treatment and diagnosis, and on testing availability.

# Summary

## Additional Information

### What Is AD?

AD is an irreversible degenerative disorder of the brain and the most common cause of dementia. As the disease advances, patients experience worsening cognitive decline, including memory loss, increasing difficulty performing daily activities, and changes in behaviour and functioning. In its later stages, AD leads to a loss of independence and complete dependence on caregivers for support. As of January 2024, an estimated 733,040 people in Canada were living with dementia.

### Unmet Needs in AD

There is an unmet need for treatments that modify the underlying course of AD and slow disease progression, preserve cognitive function and ability to perform daily activities, delay behavioural and functional decline and the need for long-term care, and maintain quality of life for both patients and their caregivers.

### How Much Does Leqembi Cost?

Treatment with Leqembi is expected to cost approximately \$38,563 per patient per year, based on a patient weight of 75 kg.

## Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that lecanemab be reimbursed for the treatment of patients with a clinical diagnosis of mild cognitive impairment (MCI) or mild dementia due to Alzheimer disease (AD) (early AD) who are *APOE* epsilon 4 (*APOE*4) noncarriers or heterozygotes, and who have confirmed amyloid pathology, only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

CDEC reviewed evidence from 1 phase III, double-blind, randomized, placebo-controlled trial (the Clarity AD trial [N = 1,795]), which enrolled patients with early AD and confirmed amyloid pathology across all *APOE*4 genotypes (i.e., *APOE*4 noncarriers, heterozygotes, and homozygotes). Specifically, the committee considered the results of post hoc analyses for patients who were *APOE*4 noncarriers or heterozygotes (N = 1,521), in accordance with the approved Health Canada indication and the sponsor's reimbursement request. The evidence demonstrated that, compared with placebo, treatment with lecanemab may result in less cognitive and functional decline in adults with MCI or mild dementia due to AD who are *APOE*4 noncarriers or heterozygotes, as measured by the change from baseline in Clinical Dementia Rating – Sum of Boxes (CDR-SB) and Alzheimer's Disease Assessment Scale – 14-Item Cognitive Subscale (ADAS-Cog14) scores at 18 months. The CDR-SB provides the sum score of 6 cognitive or functional domains, with a range of 0 to 18. The ADAS-Cog14 is a measure of cognition with a score ranging from 0 to 90. For both scales, higher scores indicate more severe impairment. The adjusted mean difference between groups in CDR-SB score was –0.579 (95% confidence interval [CI], –0.811 to –0.347;  $P < 0.00001$ ). CDEC noted that, because no established between-group minimal important difference (MID) exists, the review by Canada's Drug Agency (CDA-AMC) used a 0.5-point cumulative change on the CDR-SB as the between-group MID, and it was supported by the clinical experts consulted for the review. The 0.5-point cumulative change reflects the minimum change on the CDR-SB scale associated with a within-patient transition between disease states in MCI or the early stages of mild dementia due to AD. CDEC observed that although the estimated mean difference of –0.579 in the Clarity AD trial exceeded the proposed 0.5-point MID, the certainty of the evidence was rated as low due to imprecision and inconsistency. The CI crosses the 0.5-point threshold, with the lower bound (–0.811) suggesting a clinically meaningful effect, while the upper bound (–0.347) does not reach the proposed MID. As a result, there is imprecision and uncertainty in the effect estimate, given that the true effect may or may not be clinically meaningful. CDEC also noted that the published literature reports a wide range of within-patient MID estimates for the CDR-SB, from approximately 0.5 to 1.08 cumulative points for MCI and from 1.68 to 2 cumulative points for mild dementia due to AD. The committee reasoned that because the Clarity AD trial enrolled a population spanning both MCI and mild dementia due to AD, the true threshold for a clinically important difference at the group level may be higher than the 0.5-point cumulative MID. CDEC also considered the observed differences in the treatment effect size for the CDR-SB across the relevant subgroups, which introduces additional uncertainty about identifying patients for whom the drug will be suitable. The clinical experts consulted by CDA-AMC noted to CDEC that a 0.5-point change could represent a meaningful difference in cognition and function, and therefore

considered it a meaningful threshold in early AD. The committee also noted that the clinician group input also supported a 0.5-point change as clinically meaningful in early AD.

For the ADAS-Cog14, the adjusted mean difference between groups was  $-1.633$  (95% CI,  $-2.555$  to  $-0.712$ ;  $P = 0.00052$ ). In the absence of a between-group or within-group MID for the ADAS-Cog14, the committee could not determine whether the treatment effect of lecanemab for this end point was clinically meaningful. As with the CDR-SB, the results of subgroup analyses for the ADAS-Cog14 showed differences in the magnitude of treatment benefit.

CDEC considered evidence regarding important harms from the Clarity AD trial, including evidence that lecanemab likely results in a higher frequency of amyloid-related imaging abnormality (ARIA) events when compared with placebo. ARIA with edema or effusion (ARIA-E) events were reported in 8.9% of patients in the lecanemab group and 1.3% of patients in the placebo group. ARIA with microhemorrhage and hemosiderin deposit (ARIA-H) events occurred in 12.9% and 6.8% of patients in the lecanemab and placebo groups, respectively. At least 1 serious adverse event (SAE), excluding death, was experienced by 14.0% of patients in the lecanemab group compared to 10.3% of patients in the placebo group. CDEC acknowledged the adverse events (AEs) associated with lecanemab treatment; however, CDEC recognized that patients with early AD are faced with a progressive and ultimately debilitating condition for which there are limited treatment options. The committee discussed patient autonomy in making informed decisions about treatment in consultation with their health care team regarding the potential benefits and risks.

Health-related quality of life (HRQoL) was reported by patients and caregivers and assessed using the Quality of Life in Alzheimer's Disease (QoL-AD) measure. The adjusted mean change in QoL-AD score at 18 months was  $-0.586$  in the lecanemab group and  $-1.258$  in the placebo group, with a between-group difference of  $0.672$  (95% CI,  $0.209$  to  $1.136$ ). CDEC noted that the certainty in the evidence was low, due to the risk of bias arising from substantial missing data ( $> 10\%$ ) and imprecision. The committee noted that the adjusted mean change in caregiver burden from baseline to 18 months, assessed using Zarit Burden Interview (ZBI) score, was  $3.644$  (standard error [SE] =  $0.433$ ) in the lecanemab group and  $5.925$  (SE =  $0.427$ ) in the placebo group, with a between-group difference of  $-2.281$  (95% CI,  $-3.389$  to  $-1.173$ ). CDEC observed that the certainty of evidence regarding caregiver burden was rated as very low because the assessment instrument was not developed or validated for early AD, and there was a substantial amount of missing data ( $> 10\%$ ) and imprecision in the estimates. CDEC also observed that both QoL-AD score and ZBI score were exploratory outcomes and that the scales have no MIDs.

During the reconsideration meeting, CDEC also reviewed the sponsor's feedback that the conclusion of uncertain clinical meaningfulness in the initial recommendation rests on the misapplication of MIDs. The committee considered the sponsor's request to align clinical meaningfulness with the consensus of clinical experts and the conclusions of the CDA-AMC Clinical Review in the reconsideration. CDEC also considered feedback from clinician groups and input from clinical experts and panellists consulted for the CDA-AMC review, which consistently indicated that a 0.5-point change represents a clinically meaningful difference in the early stages of AD. CDEC discussed the 0.5-point between-group MID for the CDR-SB in the context of the  $-0.579$ -point estimate, noting uncertainty due to imprecision, as the upper bound of the CI did not

reach the MID. The committee noted that CDA-AMC removed the rating down for inconsistency that had been applied due to differences in treatment effects among subgroups, acknowledging that the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology discusses assessment of inconsistency across studies and not within a single study. CDEC noted that this resulted in a change in the certainty of evidence for the CDR-SB and ADAS-Cog14 from low to moderate. CDEC determined that recent changes in the certainty of evidence in the GRADE assessments for the CDR-SB (the primary outcome) and the ADAS-Cog14 (the key secondary outcome) suggest that lecanemab is likely to provide meaningful benefit in addressing some unmet needs in early AD such as delaying progression, which may result in lessening caregiver burden.

CDEC noted that patients and their families and/or caregivers identified an unmet need for disease-modifying treatments for AD that can slow disease progression, help preserve cognition and daily functioning, delay behavioural changes and long-term care placement, and maintain quality of life for both patients and their caregivers. The committee also acknowledged the limited pharmacologic treatment options for patients with a clinical diagnosis of MCI or mild dementia due to AD. However, CDEC determined that the limitations regarding the imprecision of the estimated treatment effect and the observed differences in subgroup findings, as well as the unclear MID thresholds, make it challenging to conclusively determine a clinically meaningful benefit of lecanemab in reducing cognitive or functional decline in the intended patients. CDEC also decided that the certainty in the evidence was too low to conclusively determine a clinically meaningful effect of lecanemab on HRQoL or caregiver burden. The committee also noted that the new sensitivity analyses submitted by the sponsor for the HRQoL and caregiver burden end points demonstrated the robustness of these findings to missing data. Accordingly, CDA-AMC removed the GRADE downgrade for risk of bias due to missing data, resulting in a change in certainty of evidence from low to moderate for the QoL-AD and from very low to low for the ZBI, indicating that lecanemab may result in less worsening of caregiver burden when compared with placebo.

During the initial and reconsideration meetings, CDEC recognized the significant unmet need in early AD, given the condition's severity, progressive decline, risk of institutionalization, limited treatment options, and associated caregiver burden. Given the evidence reviewed during the initial deliberation and the newly submitted evidence that was discussed during the reconsideration meeting, CDEC concluded that lecanemab may address a significant unmet clinical need to a degree that justifies a positive recommendation despite the uncertainty in the clinical value.

Using the sponsor-submitted price for lecanemab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for lecanemab was \$288,760 per quality-adjusted life-year (QALY) gained compared with standard of care using a health care payer perspective. If adopting a societal perspective, which includes HRQoL impacts on informal caregivers and patient out-of-pocket costs, the ICER is \$265,505 per QALY gained. At these ICERs, lecanemab is not cost-effective at a \$50,000-per-QALY-gained willingness-to-pay (WTP) threshold for the indicated population. A price reduction is required.

**Table 1: Reimbursement Conditions and Reasons**

| Reimbursement condition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Reason                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Implementation guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| <b>Initiation</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p>1. Treatment with lecanemab should be reimbursed for adult patients with MCI or mild dementia due to AD with all of the following criteria:</p> <ul style="list-style-type: none"> <li>1.1. APOE4 noncarrier or heterozygote</li> <li>1.2. confirmed amyloid pathology using amyloid PET scan, CSF analysis, or equivalent validated method</li> <li>1.3. age 50 years or older.</li> </ul>                                                                                                                                                                                                                                                                                                                                                             | <p>Evidence from the Clarity AD trial demonstrated reduced cognitive and functional decline with lecanemab treatment in patients aged 50 to 90 years with these characteristics.</p> <p>According to the Health Canada indication, treatment with lecanemab is approved for patients who are APOE4 noncarriers or heterozygotes.</p> <p>According to the product monograph for lecanemab, the presence of amyloid beta pathology must be confirmed using approved methods such as amyloid PET scan, CSF analysis, or equivalent validated methods before initiating treatment with lecanemab.</p> | <p>Although the Clarity AD trial enrolled patients with an MMSE score of 22 to 30 at baseline, CDEC agreed with the clinical experts consulted by CDA-AMC that, for cognitive assessment, alternative memory assessment scales accepted for use in clinical practice (e.g., the MoCA) may be used to confirm MCI or mild dementia due to AD in clinical practice.</p> <p>The participating drug programs have requested clarification on which specific memory assessment scales would be appropriate for the purposes of identifying patients with MCI or mild dementia due to AD, along with the thresholds that should be used for each of those scales. CDA-AMC considered this feedback and concluded that this exceeds the scope of a Reimbursement Review, and has advised that a panel of specialists be convened to provide detailed advice on those diagnostic conditions.</p> |
| <b>Renewal</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p>2. Reimbursement of treatment with lecanemab should be continued after the initial 6 months of treatment, and then every 12 months if all of the following conditions are met:</p> <ul style="list-style-type: none"> <li>2.1. There is evidence of ongoing benefit, such that the patient has not progressed to moderate dementia (e.g. MMSE score &lt; 20 or MoCA score &lt; 17, or equivalent reflecting the upper threshold for moderate dementia).</li> <li>2.2. Patient safety can be ensured, meaning the patient is able to adhere to the required MRI monitoring schedule before the third, fifth, seventh, and 14th doses (approximately on days 28, 56, 84, and 182), with treatment discontinued for patients who do not undergo</li> </ul> | <p>The product monograph for lecanemab states that treatment with lecanemab should be discontinued if the patient progresses to moderate AD.</p> <p>The clinical experts consulted by CDA-AMC agreed that lecanemab should be discontinued if there is evidence of disease progression to a moderate or worse stage of dementia.</p>                                                                                                                                                                                                                                                              | <p>The clinical experts consulted by CDA-AMC stated that response to treatment should be assessed every 6 to 12 months.</p> <p>CDEC agreed with the clinical experts consulted by CDA-AMC that alternative assessment scales may be used to monitor progression to a moderate or worse stage of dementia. CDA-AMC is advising jurisdictions that guidance on the assessment scales and the appropriate thresholds for each scale could be addressed in the aforementioned implementation panel.</p> <p>CDEC also agreed with the clinical experts that treatment with lecanemab should be discontinued in patients experiencing macrohemorrhage, 1 area of superficial siderosis, more than 10 microhemorrhages since initiation of treatment, or more than 2 episodes of ARIA.</p>                                                                                                      |

| Reimbursement condition                                                                                                                                                                                                                                                                                                                       | Reason                                                                                                                                                                                                                                                                                                                                                                                                                       | Implementation guidance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <p>MRI surveillance.</p> <p>2.3. Patient does not exhibit symptomatic ARIA or moderate to severe radiographic ARIA.</p> <p>2.4. The product monograph for lecanemab provides MRI classification criteria for severity of radiographic ARIA.</p>                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Prescribing</b>                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>3. Lecanemab should be prescribed by clinicians with expertise and experience in diagnosing, managing, and treating patients with AD, with timely access to MRI.</p> <p>4. Lecanemab infusions should be administered by qualified health care professionals trained to monitor for, recognize, and manage infusion-related reactions.</p> | <p>This is meant to ensure that lecanemab is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.</p>                                                                                                                                                                                                                                                                 | <p>CDEC noted that the product monograph for lecanemab recommends obtaining an MRI before the third, fifth, seventh, and 14th infusions. Additionally, if a patient develops symptoms suggestive of ARIA, a clinical evaluation, including an MRI, should be performed. CDEC agreed that the prescribing clinician should ensure that the required MRI monitoring would be available before initiating treatment with lecanemab.</p> <p>Jurisdictions may consider requiring that, in addition to having expertise and experience in the diagnosis, management, and treatment of patients with AD (and timely access to MRI), clinicians complete training on the recognition and management of ARIA, such as the sponsor-provided ARIA educational program, before prescribing lecanemab.</p> |
| <p>5. Lecanemab should not be used in combination with other monoclonal antibody therapies for AD.</p>                                                                                                                                                                                                                                        | <p>The Clarity AD trial did not combine lecanemab with other monoclonal antibody therapies for AD, and CDEC did not review any evidence regarding the efficacy and safety of lecanemab when used in combination with these therapies.</p>                                                                                                                                                                                    | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Pricing</b>                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>6. A reduction in price.</p>                                                                                                                                                                                                                                                                                                               | <p>The ICER for lecanemab is \$288,760 per QALY gained when compared with standard of care using a health care payer perspective. This decreases to \$265,505 per QALY gained when adopting a societal perspective.</p> <p>A price reduction greater than 90% would be required for lecanemab to achieve an ICER of \$50,000 per QALY gained compared to standard of care when adopting a health care payer perspective.</p> | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Reimbursement condition                                                                                                                                                                                                                                                                                                                                                                                                                            | Reason                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Implementation guidance                                                                                                                                                                                                                                                                    |
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|                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <p>A smaller price reduction is required to achieve cost-effectiveness at a \$50,000 per QALY gained threshold if a societal perspective is adopted.</p> <p>Price reductions for different thresholds for both perspectives are available in the Pharmacoeconomic Review report.</p>                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                            |
| <b>Feasibility of adoption</b>                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                            |
| 7. The economic feasibility of adoption of lecanemab must be addressed.                                                                                                                                                                                                                                                                                                                                                                            | At the submitted price, the incremental budget impact of lecanemab is expected to be greater than \$40 million in years 1, 2, and 3.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | —                                                                                                                                                                                                                                                                                          |
| <p>8. The following will pose significant challenges to the organizational feasibility of adopting lecanemab into the health system:</p> <p>8.1. access to MRIs for monitoring ARIA events</p> <p>8.2. access to physicians with expertise in the diagnosis of MCI and mild dementia, and access to associated resources (e.g., validated methods to confirm amyloid pathology) to determine patient eligibility for treatment with lecanemab.</p> | <p>Monitoring for ARIA events associated with lecanemab requires clinical and MRI resources not routinely needed in the care of patients with AD. Access to these resources will be challenging due to capacity constraints.</p> <p>The scope of the CDA-AMC review did not evaluate the potential impact of allocating MRI resources to meet the monitoring requirements for lecanemab on the wait times or health outcomes for those with other health conditions for which MRI is warranted.</p> <p>Jurisdictions will need to consider these factors when evaluating the feasibility of providing reimbursement for lecanemab.</p> | A sponsor-funded or sponsor-supported registry, developed in collaboration with clinicians, patients, and provincial and territorial jurisdictions, should be established to capture data on utilization (including IV dosing), cognitive outcomes, safety, and patient-reported outcomes. |

AD = Alzheimer disease; ARIA = amyloid-related imaging abnormality; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CSF = cerebrospinal fluid; ICER = incremental cost-effectiveness ratio; MCI = mild cognitive impairment; MMSE = Mini Mental State Exam; MoCA = Montreal Cognitive Assessment; QALY = quality-adjusted life-year.

## Discussion Points

- Reconsideration request:** The sponsor requested a major reconsideration of the initial draft recommendation to not reimburse lecanemab for the treatment of patients with a clinical diagnosis of MCI or mild dementia due to AD (early AD) who are APOE4 noncarriers or heterozygotes and who have confirmed amyloid pathology. There were 6 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The sponsor highlighted that CDEC overemphasized tolerability and accessibility and did not fully consider the CDA-AMC framework in assessing unmet needs, and that the conclusions of the initial recommendation focused on select outcomes (CDR-SB and ADAS-Cog14 scores) and not the totality of submitted evidence. The sponsor contended that conclusions about uncertain clinical meaningfulness were based on misapplied MID, imprecision, and inappropriate subgroup analyses. The sponsor was of the opinion that the inconsistency rating based on exploratory and underpowered subgroup analyses did not align with core GRADE methodology.

They submitted 48-month data from the Clarity AD open-label extension (OLE) and clarifications regarding the Alzheimer Disease Neuroimaging Initiative (ADNI) comparison to address concerns regarding the uncertainty in the long-term benefit of lecanemab. The sponsor also submitted additional real-world evidence to address concerns about safety, ARIA risk, and MRI monitoring feasibility.

- **Unmet needs:** During the initial meeting, CDEC noted that patient groups identified an unmet need for treatments that delay behavioural changes and long-term care placement, and noted that the evidence reviewed was insufficient to determine whether lecanemab meets these needs. Clinicians also identified an unmet need for therapies that are better tolerated and more accessible. CDEC determined that it was uncertain whether lecanemab meets the need for better tolerated therapies (given the risk of ARIA events and infusion-related reactions with lecanemab) or the need for more accessible treatments (due to the need for biweekly IV administration and safety monitoring requirements). During the reconsideration meeting, CDEC acknowledged that the revised GRADE assessments led to improved certainty in the evidence for the primary and key secondary end points, suggesting that lecanemab is likely to provide meaningful benefit in addressing some unmet needs of patients with early AD and their caregivers.
- **Appropriate population:** CDEC noted that younger patients with early AD may present differently and may progress differently than older patients. The committee discussed the fact that the Clarity AD trial enrolled patients aged 50 to 90 years, and noted the current absence of evidence regarding the efficacy and safety of lecanemab in younger patients.
- **Uncertainty with proposed MID:** During the initial meeting, CDEC noted that the CDR-SB score reflects performance across all instrument domains and acknowledged the clinical experts' input that the MID requires a smaller score change in patients with MCI than in patients with moderate or worse stages of dementia, although such a change may carry greater clinical significance in the population with MCI. CDEC discussed that there is no published between-group MID for the CDR-SB scale, and because the within-patient MID estimates for the instrument vary widely across MCI and mild dementia, the true between-group threshold for clinical importance in the Clarity AD population may exceed the proposed 0.5-point threshold. The clinical experts highlighted that a clinically meaningful change could represent an improvement in any of the 6 domains of CDR-SB scale. CDEC discussed the domain-specific scores available for the indicated subgroup and observed that the overall CDR-SB difference of  $-0.579$  (95% CI,  $-0.811$  to  $-0.347$ ) in APOE4 noncarriers and heterozygotes did not appear to be driven by data from a single domain. During the reconsideration meeting, CDEC considered the sponsor's concerns about misapplication of MID and noted that in the absence of a published or widely accepted between-group MIDs, CDA-AMC reviewers draw on the best available evidence and input from clinical experts to define a threshold that reflects meaningful change in clinical practice. The clinical experts consulted by CDA-AMC agreed that a 0.5-point change could represent a difference in cognition and function, and therefore considered it a meaningful threshold in early AD. The committee noted that the clinician groups' feedback also supported a 0.5-point change as clinically meaningful in early AD.

- **Certainty of evidence:** During the initial meeting, CDEC discussed the certainty of evidence as assessed using the GRADE method. The committee noted that the certainty of evidence was generally low due to various reasons, including imprecision, inconsistency, and substantial missing data for some outcomes that might have introduced bias. The committee also noted that the CDA-AMC review rated the evidence down for some, but not all, identified limitations. CDEC considered whether exemptions could be made to accommodate the level of uncertainty in the evidence but determined that the disease under review (MCI and mild dementia due to AD) does not meet the criteria in the *Procedures for Reimbursement Reviews* for such allowances. During the reconsideration meeting, CDEC reviewed the sponsor's feedback regarding the downgraded certainty for the CDR-SB and ADAS-Cog14 end points due to inconsistency. The sponsor noted that this assessment was based on exploratory, underpowered, within-trial subgroups and did not align with core GRADE methodology. The sponsor submitted that the core GRADE approach primarily discusses assessment of inconsistency across studies and cautions against downgrading in the absence of credible, prespecified subgroup effects. The committee noted that CDA-AMC had removed the GRADE downgrades in the certainty of evidence, acknowledging that the subgroup analyses were performed using data from a single trial. CDEC acknowledged that definitive conclusions about the treatment benefits in subgroups are not possible; however, the committee noted that reporting differences in the subgroup results is useful for awareness of potential variability in the magnitude of benefit across study populations, which may have implications for selecting patients for whom treatment with lecanemab would result in optimal benefit. The committee also noted that the new sensitivity analyses submitted by the sponsor for the HRQoL and caregiver burden end points demonstrated the robustness of these findings to missing data. Accordingly, CDA-AMC removed the GRADE downgrade for risk of bias due to missing data, resulting in a change in the certainty of evidence from low to moderate for the QoL-AD and from very low to low for the ZBI.
- **Other efficacy results:** During the initial meeting, CDEC acknowledged that the Alzheimer's Disease Composite Score (ADCOMS) and Alzheimer's Disease Cooperative Study Mild Cognitive Impairment – Activities of Daily Living (ADCS MCI-ADL) results from the Clarity AD trial, evaluating cognition and function, trended in the same direction as the CDR-SB and ADAS-Cog14, supporting the effect of lecanemab on cognitive and functional outcomes. During the reconsideration meeting, CDEC considered the sponsor's feedback that the initial recommendation focused on mean changes in CDR-SB and ADAS-Cog14 scores without incorporating prespecified cognitive and functional end points important to patients (e.g., ADCS MCI-ADL score, rate of change, and time to worsening [TTW]), which the sponsor indicated consistently favoured lecanemab and demonstrated a clinically relevant pattern of benefit. The committee noted that outcomes included in reviews are typically prespecified based on input from patient groups, clinician groups, and clinical experts consulted by CDA-AMC, and that not all outcomes in a sponsor's submission are required for reimbursement decision-making. CDEC also noted that results for other key secondary end points (ADCOMS and ADCS MCI-ADL scores) were reported in the appendices and addressed in the Discussion and Conclusions sections of the CDA-AMC Clinical Review report.

- Long-term efficacy:** During the initial meeting, CDEC reviewed findings from the OLE study, the Clarity AD OLE study, which assessed changes in CDR-SB scores among patients who continued lecanemab treatment beyond the initial 18-month core study and compared to findings from the ADNI, an observational study. The committee discussed whether the comparison with the ADNI study was appropriate. CDEC acknowledged clinical expert input indicating that the ADNI study is a well-established natural history study and represents the best available external comparator. After 18 months in the extension phase (i.e., 36 months total follow-up from the core study baseline), the adjusted mean difference in CDR-SB score change between groups was  $-0.774$  (95% CI not reported) in favour of lecanemab over the ADNI findings. CDEC noted the clinical experts' observation that patients in the ADNI study were generally less likely to experience rapid clinical deterioration or develop behavioural symptoms, suggesting that the observed difference between lecanemab and ADNI groups in the OLE may be underestimated. However, CDEC concluded that the certainty of this evidence was low due to several limitations, including the lack of methodological detail on the matching procedures with the ADNI cohort, the absence of validation demonstrating cohort comparability, imbalances in baseline characteristics, high attrition rates ( $> 30\%$  in each group), potential selection bias associated with the OLE enrolment method, and the use of descriptive analyses without measures of variability. During the reconsideration meeting, CDEC reviewed the new 48-month OLE results and methodological clarifications provided by the sponsor to address concerns from the initial recommendation regarding the Clarity AD OLE and ADNI study methods, and duration of follow-up. The committee noted that at 48 months, the difference in change from baseline in CDR-SB scores between the Clarity AD OLE and ADNI cohorts was  $-1.308$  (95% CI,  $-2.166$  to  $-0.450$ ), suggesting an increasing treatment effect compared with earlier time points (18 months and 36 months). However, the committee noted limitations with the analysis, including matching methodology and adequacy, and attrition and handling of missing data. CDEC noted baseline imbalances in CDR-SB scores between the groups and recalled evidence from the Clarity AD trial indicating that patients with more severe baseline scores tended to experience greater mean changes in CDR-SB scores, as observed in subgroup analyses comparing MCI and mild dementia due to AD, for which changes in the mild dementia subgroup were larger. Thus, it was unclear whether the observed increase in treatment effect was fully attributable to lecanemab or partly due to differences in baseline disease severity.
- Harms:** During the initial meeting, CDEC noted the increased frequency of ARIA events with lecanemab and discussed how limited MRI access in some provinces may affect monitoring. Clinical experts indicated that several practical approaches could help mitigate this concern, such as using a shorter 10-minute MRI sequence, prioritizing MRI availability based on clinical urgency rather than queue order, and requiring MRI before dosing. They noted that limited access would mainly delay subsequent doses rather than increase safety risk. The clinical experts also emphasized that most ARIA events occur early, which means substantially reduced need for routine MRI monitoring after the first 6 months, as imaging becomes primarily symptom-driven. However, CDEC observed that although 90% of ARIA-E events occurred within the first 6 months of the Clarity AD trial and ARIA-H events were distributed throughout the 18-month treatment period, there remains a lack of critically

appraised evidence regarding the long-term safety of lecanemab beyond 36 months, despite the chronic nature of the condition under review. During the reconsideration meeting, CDEC reviewed harms data at 48 months from the Clarity AD OLE trial. The committee noted that the safety profile of lecanemab remains an important consideration, given the frequency and severity of some of the observed AE data, such as SAEs requiring hospitalization or prolongation of existing hospitalization, TEAEs leading to dose interruption and study drug withdrawal, treatment-emergent deaths, ARIA-E, ARIA-H, and macrohemorrhage. However, CDEC recognized that patients with early AD are faced with a progressive and ultimately debilitating condition for which there are limited treatment options. The committee discussed patient autonomy in making informed decisions about treatment in consultation with their health care team regarding the potential benefits and risks.

- **Gaps in the evidence:** CDEC noted that the Clarity AD trial did not provide evidence on the optimal duration of lecanemab treatment or criteria for discontinuation. The committee discussed a sponsor-submitted study to address this gap, which examined an off-treatment interval between 2 phases of a phase 2b study, during which patients stopped lecanemab. The CDR-SB results showed similar rates of clinical progression in patients previously treated with lecanemab and those who had received placebo. Furthermore, brain amyloid reaccumulation was observed in patients who had discontinued lecanemab therapy. The sponsor suggested that these findings support the need for continued treatment to maintain amyloid suppression and clinical benefits of delayed disease progression. However, CDEC determined that the study had several limitations and was insufficient to draw firm conclusions about cognitive outcomes following discontinuation of lecanemab therapy. CDEC agreed with the clinical experts that treatment with lecanemab should be discontinued upon disease progression to a moderate or worse stage of dementia.
- **Amyloid PET and cerebrospinal fluid (CSF) testing:** CDEC noted that confirmation of amyloid pathology is required for initiation of treatment with lecanemab. The committee discussed the fact that there are disparities in amyloid PET access and variability in reimbursement of amyloid PET and CSF AD biomarker testing across jurisdictions in Canada, which leads to inequities in access. CDEC also received input from clinical experts that the field is moving at a fast pace and many developments are under way in Canada, including the availability of blood biomarkers that are used in some jurisdictions.
- **APOE testing:** *APOE* genotype testing is not currently performed as part of routine testing for early AD in Canada. The committee noted that because the testing infrastructure for *APOE* genotype testing is already established, any additional “medically necessary” indications in Canada for *APOE* genotyping (e.g., anti-amyloid beta treatment eligibility and ARIA risk assessment) would be feasible and would not likely significantly impact human or health care resources.
- **MRI monitoring:** During the initial meeting, CDEC noted input from clinical experts regarding the need for close monitoring for ARIA events and the MRI monitoring requirements from the lecanemab product monograph. The committee discussed MRI capacity constraints that exist in various provinces across the country, including limited and variable availability of timely access to MRI — which may pose challenges for safe and equitable treatment initiation — and adequate monitoring for

all eligible patients. System capacity constraints along the continuum of care for AD raise questions of who will be responsible for prioritizing eligible patients for access to treatment and supporting infrastructures. The committee also noted that a 10-minute MRI sequence can screen for ARIA, which could help to mitigate capacity constraints. The committee noted concerns regarding current resources, and that health care system changes would be required to accommodate the required monitoring. During the reconsideration meeting, CDEC considered real-world evidence submitted by the sponsor on ARIA events and the feasibility of MRI monitoring. While the committee was unable to draw definitive conclusions from this evidence, it acknowledged that the findings were consistent with observations from the Clarity AD trial and clinical expert input indicating that ARIA events most often occur early in the course of treatment. CDEC also noted expert input indicating that, although MRI monitoring is important during the initial stages of lecanemab treatment, the need for monitoring decreases over time. The committee further discussed the fact that MRI capacity remains a practical consideration across jurisdictions.

- **Ethics and equity:** During the initial meeting, CDEC acknowledged that several groups (including women, Indigenous Peoples, and racialized populations) are disproportionately impacted by AD. They noted current systems-level gaps in current AD diagnosis, care, and management in Canada, and how these gaps tend to be exacerbated for those in rural or remote areas, and for racialized and other equity-deserving groups. The committee discussed how the implementation of lecanemab would require expanding and reorganizing health system resource capacity in Canada to support timely, safe, appropriate, and equitable access. The committee discussed the principle of proportionality, in relation to the balance of benefits and harms of lecanemab, and also noted relevant health system challenges that should inform system-level planning. During the reconsideration meeting, the committee discussed the importance of enabling patient choice in weighing the balance of harms and benefits of lecanemab, including administration and monitoring requirements. They also discussed the overall limited population of patients with MCI or early AD who would be eligible for treatment with lecanemab, and resource allocation challenges associated with providing this therapy alongside meeting the needs of those who are ineligible.
- **Societal value:** During the reconsideration meeting, the committee noted that treatment with lecanemab may have an important impact on caregiver HRQoL and patient out-of-pocket costs as a result of the delayed progression of AD. CDA-AMC presented a cost-effectiveness analysis adopting a societal perspective that included impacts on informal caregiver HRQoL and out-of-pocket costs incurred by patients. The committee agreed that there was sufficient evidence to support the conclusion that there may be an impact on these outcomes.
- **Economic considerations:** The committee discussed the costs associated with diagnosing, monitoring, and administering lecanemab. The committee discussed the impacts on cost-effectiveness as highlighted by a CDA-AMC scenario analysis in the pharmacoeconomic report, which removed administration costs under the assumption that these were not incurred by the public payer. In this analysis, incremental costs for patients receiving lecanemab versus standard of care decreased by approximately \$19,000 per patient.

## Background

AD is a progressive, irreversible neurodegenerative disorder and the most common cause of dementia. The understanding of AD pathogenesis is evolving; both overproduction and/or decreased removal of amyloid beta peptides in the brain and involvement of a microtubule-associated protein, tau, have been associated with the pathogenesis of AD. The prevalence of AD increases with advancing age, with AD primarily affecting individuals older than 65 years. Several risk factors have been associated with developing AD, including the presence of genetic traits, family history of dementia, brain trauma, the presence of certain chronic conditions, and dietary or lifestyle factors. One such established genetic risk factor is *APOE*, with individuals with 1 or 2 epsilon 4 alleles (*APOE4*) being at increased odds of developing AD compared with noncarriers. In January 2024, an estimated 733,040 people were living with dementia in Canada.

AD clinical staging comprises categories of MCI due to AD and dementia due to AD (which is divided into mild, moderate, and severe stages). The clinical stages of AD progress on a continuum, with increasingly evident cognitive dysfunction and the development and progression of functional impairment. Clinical symptoms are initially apparent in the MCI due to AD stage, which are characterized not only by impairment of cognitive abilities such as memory, but also language and executive and visuospatial function. Individuals are essentially still able to perform normal functional activities independently at this stage. With progression to dementia due to AD, the mild phase is characterized by further memory loss and other cognitive deficits, some difficulties with functioning, and behaviour changes. Individuals are no longer fully independent and require some assistance with daily activities. Progression through the stages of moderate and severe dementia due to AD involves increasing and serious functional and cognitive impairment with patients ultimately becoming unable to communicate and completely dependent on others for their care.

In individuals living with AD, quality of life may be negatively impacted by factors such as impaired cognition, reduced social activities, psychiatric comorbidities, and reduced functionality. Caregiver tasks and responsibilities can negatively impact caregiver health and quality of life, and may have detrimental effects on financial well-being.

Current treatments indicated for AD in Canada include cholinesterase inhibitors (ChEIs) (e.g., donepezil, galantamine, and rivastigmine) and memantine. These medications are approved for use in patients with dementia due to AD (the indicated medication varies by severity of dementia), but none are approved for use in patients with MCI due to AD. ChEIs and memantine target symptoms associated with cognitive decline and do not alter the course of the underlying dementia. There is an unmet need for treatment that modifies the underlying disease mechanism in AD and slows disease progression.

In the sponsor's initial submission to Health Canada and to CDA-AMC, the proposed indication for lecanemab was "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." A Notice of Non-Compliance (NON) was issued by Health Canada citing clinical efficacy and safety concerns, which included an unfavourable risk-benefit profile in patients who are *APOE4* carriers (noting that *APOE4* homozygotes did not benefit from treatment). The sponsor subsequently proposed that lecanemab be indicated for use in patients with early AD who are *APOE4* noncarriers and heterozygotes and a Notice

of Compliance with Conditions (NOC/c) was granted by Health Canada for lecanemab on October 24, 2025, in which the approved indication was limited to patients with early AD who are APOE4 noncarriers or heterozygotes. The Health Canada conditionally approved indication for lecanemab is “for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment or mild dementia due to Alzheimer’s disease (early Alzheimer’s disease) who are apolipoprotein E epsilon 4 (ApoE epsilon 4) noncarriers or heterozygotes, and who have confirmed amyloid pathology.” Lecanemab is a humanized IgG1 monoclonal antibody. It is available as a 100 mg/mL solution for IV infusion and the dosage recommended in the product monograph is 10 mg/kg once every 2 weeks.

## Sources of Information Used by the Committee

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

- a review of results from 1 phase III, multicentre, randomized, double-blind, placebo-controlled, parallel-group study in adult patients with MCI due to AD or mild dementia due to AD; 1 long-term extension study; and 1 study addressing gaps in the systematic review evidence
- patients’ perspectives gathered by 3 patient groups (the Alzheimer Society of Canada, the Alzheimer Society of Ontario, and Dementia Network Calgary)
- input from public drug plans that participate in the reimbursement review process
- 5 clinical specialists with expertise diagnosing and treating patients with MCI due to AD or mild dementia due to AD and 1 clinical chemist with expertise in *APOE* genotype testing in Canada
- input from 4 clinician groups (the Canadian Consortium on Neurodegeneration in Aging, Clinique Interdisciplinaire de Mémoire du CHU de Québec, the Consortium of Canadian Centres for Clinical Cognitive Research, and Geriatricians at Trillium Health Partners)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to lecanemab
- a review of testing procedure considerations for *APOE* genotype testing in Canada for adults with a clinical diagnosis of MCI or mild dementia due to AD
- information submitted as part of the sponsor’s request for reconsideration (described subsequently)
- feedback on the draft recommendation.

## Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to the CDA-AMC call for input and from clinical experts consulted by CDA-AMC for the purpose of this review. Input was received from patient and clinician groups at the time when the proposed indication included patients of all APOE4 carrier types (i.e., APOE4 noncarriers, heterozygotes, and homozygotes).

No additional input was received from the patient or clinician groups after the NOC/c was granted by Health Canada, which restricts the indicated population to patients who are APOE4 noncarriers and heterozygotes.

## Patient Input

Three patient groups provided input for this review: the Alzheimer Society of Canada, the Alzheimer Society of Ontario, and Dementia Network Calgary. These groups collected input from people with MCI or dementia as well as caregivers.

Patient groups reported that AD and dementia had significantly impacted their day-to-day life and quality of life. Patients communicated that AD had upended their daily lives, disrupted their retirement plans and robbed them of time, caused a loss of independence, changed their relationships with others, and caused worry over the unpredictability of AD and the lack of control. Input highlighted that AD eventually affects all aspects of a person's life with increasing levels of medical and social care needed as the disease progresses. Patients and caregivers reported increased use of services (e.g., day programs, respite services, home care) upon progression of AD, with some reporting moving into long-term care.

Caregivers reported significant physical, emotional, and financial stress as well as feelings of exhaustion, anxiety, and depression. They reported concerns surrounding the need to provide an increased amount of assistance with instrumental activities of daily living (IADLs) and activities of daily living (ADLs) over time, and giving up other aspects of their life (e.g., work, social life) to provide care. Caregivers described the heartbreaking experience of witnessing a once active and independent family member become unable to do the things they once enjoyed and be entirely dependent on others for all tasks of life as AD progresses.

Outcomes of treatment for AD identified as important by patients and caregivers included slowing of disease progression; cure or reversal of disease; and improving or maintaining cognition, function, and quality of life. Many patients and caregivers noted that access to a medication that delays progression of AD or MCI would impact their lives by allowing a longer duration of independent living, lessening or delaying caregiving responsibilities, allowing more time to prepare and adjust to changes, reducing anxiety and stress, and improving quality of life. Participants commented that trade-offs to consider in choosing a new therapy include the time, cost, and side effects associated with the medication, and expressed that they would need trusted information on potential benefits, risks, and trade-offs to make a decision.

## Clinician Input

### Input From Clinical Experts Consulted by CDA-AMC

The information in this section is based on the input received from a panel of 5 clinical specialists consulted by CDA-AMC for the purpose of this review.

According to the clinical experts, there are currently no disease-modifying treatments available in Canada that could delay disease progression. Current treatments include ChEIs and memantine, which are symptomatic therapies that provide temporary and modest improvements in function, cognition, and behaviour.

The goals of treatment for early AD, as identified by the clinical experts, are to maintain function in ADLs, stabilize or reduce cognitive decline, improve HRQoL, and improve behavioural symptoms. The experts agreed that, in contrast to moderate or worse stages of dementia, individuals in the early stages of AD are generally able to go about their lives independently with limited need for support. However, the experts noted that the burden on caregivers in the early stages of the disease is still present, even though the nature of that burden may be different. Moreover, the clinical experts indicated that preventing the need to move into a long-term care home and reducing health care and societal costs of AD are important goals of therapy.

The experts stated that lecanemab should be considered as a first-line treatment, used in combination with other pharmacological treatments for mild dementia due to AD and nonpharmacological interventions for MCI and mild dementia due to AD.

All of the clinical experts consulted by CDA-AMC reported that individuals with amnesic MCI due to AD and/or mild dementia due to AD are best suited for treatment with lecanemab, acknowledging that treatment is restricted by Health Canada to patients who are APOE4 noncarriers and heterozygotes. Individuals in the moderate and severe stages of AD would not be suitable for initiation of treatment with lecanemab, according to the experts. Diagnosis of the condition includes carefully corroborated history, cognitive testing, MRI, physical examination, and confirmation of AD pathology either by amyloid PET scan or CSF findings. According to the clinical experts, thorough clinical assessment and demonstration of amyloid positivity are critical for identifying patients who are eligible for treatment with lecanemab. The experts noted that there are disparities in access to and reimbursement for the necessary imaging assessments, and disparities in reimbursement for laboratory assessments between and within jurisdictions in Canada.

According to the clinical experts, response to treatment should be assessed every 6 to 12 months. The clinical experts agreed that the outcomes of interest include both cognitive and functional end points. The experts noted that the magnitude of treatment response that is considered clinically meaningful may vary across physicians and may be impacted by patient and caregiver factors. Additional important outcomes reported by the experts included delayed progression to moderate or severe stages of the disease, delayed loss in patients' quality of life, and reduced burden or loss in quality of life for caregivers.

The experts stated that the decision to stop treatment with lecanemab would be based on clinical judgment, results of imaging identifying harms, and discussion with patients and/or caregivers. All clinical experts agreed that lecanemab should be discontinued if there is evidence of disease progression to a moderate or worse stage of dementia. The clinical experts agreed that there is uncertainty regarding the clinical importance of the various presentations of ARIA events. Nonetheless, the clinical experts stated that lecanemab should be suspended in the case of symptomatic ARIA events and discontinued in the case of severe (radiographic or symptomatic) ARIA or repeated ARIA events. One expert added that treatment discontinuation should be considered in patients experiencing any macrohemorrhage, 1 area of superficial siderosis, more than 10 microhemorrhages since initiation of treatment, or more than 2 episodes of ARIA, or in patients who need treatment with anticoagulants.

The clinical experts agreed that a specialist in the treatment of cognitive disorders including MCI and AD would be required for diagnosis, determination of treatment eligibility, treatment initiation, and monitoring

for and treating possible AEs. Required specialties would include neurologists, geriatricians, and geriatric psychiatrists, with relevant expertise in AD diagnosis and understanding of disease-modifying medications. One clinical expert added that clinicians with extensive training in cognitive disorders, dementia, and AD could likely perform patient selection and manage treatment, if supported by specialists or memory clinics for counselling when needed for special or atypical cases.

### **Clinician Group Input**

CDA-AMC received submissions from 4 clinician groups: the Canadian Consortium on Neurodegeneration in Aging (input contributed by 4 clinicians), Clinique Interdisciplinaire de Mémoire du CHU de Québec (6 clinicians), the Consortium of Canadian Centres for Clinical Cognitive Research (6 clinicians), and Geriatricians at Trillium Health Partners (4 clinicians).

The clinician groups stated that currently available pharmacologic therapies for the treatment of AD offer modest symptomatic benefit and do not modify the course of the disease or the underlying pathologic process, and that patients will inevitably experience disease progression. It was also noted that there are currently no medications approved in Canada for the treatment of MCI due to AD. All clinician groups highlighted that there is an unmet need for treatment that modifies the underlying disease mechanism in AD. One group added that important goals of treatment include minimizing AEs; improving HRQoL; and, broadly, reducing health and social care costs associated with AD.

The clinician groups stated that lecanemab would be used first-line in patients with MCI or mild dementia due to biomarker-confirmed AD, and that patients best suited for treatment with lecanemab would reflect the patient population in the Clarity AD trial. Some clinician groups noted that APOE4 carriers are at higher risk of ARIAs and progression to dementia (if diagnosed with AD pathology), and that caution may be warranted in the treatment of APOE4 homozygotes. Testing for APOE4 status may be recommended to inform appropriate use and discussions with patients regarding the risks and benefits of treatment with lecanemab. Identification of eligible patients and prescribing and monitoring of lecanemab therapy would be performed by clinicians with expertise in the field of neurodegeneration and dementia. The clinician groups noted that prescribing of lecanemab would require significant changes to clinical practice for dementia care in Canada, including the need for testing to confirm amyloid beta pathology, MRI monitoring, and biweekly IV infusion of medication.

A variety of health care professionals — including neuroradiologists, nuclear medicine physicians, anesthesiologists, nurses, and laboratory medicine specialists — would also be required as part of the team caring for patients treated with lecanemab.

The clinician groups noted a lack of evidence regarding when to discontinue lecanemab therapy. The clinician groups recommended that lecanemab could be stopped for evidence of lack of benefit, such as progression to a moderate or worse stage of dementia; however, suggestions for the criteria that could be used varied. As per the Clarity AD study, the clinician groups recognized that discontinuation of lecanemab therapy may be required in the event of AEs such as ARIA or infusion reactions, in the event that a patient develops any of the trial exclusion criteria, or if a patient and/or substitute decision-maker wishes to discontinue the medication.

Generally, the unmet needs, treatment goals, and expectations regarding place in therapy and patient population described by clinician groups were aligned with those identified by the clinical experts consulted by CDA-AMC.

## Drug Program Input

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

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy.

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

**Table 2: Responses to Questions From the Drug Programs**

| Implementation issues                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| <b>Considerations for initiation of therapy</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>Disease diagnosis, scoring, or staging for eligibility</b></p> <p>The following were inclusion criteria (related to diagnosis, scoring, or staging) in the pivotal Clarity AD study:</p> <ul style="list-style-type: none"> <li>• demonstrate brain amyloid pathology as indicated by either a PET assessment of imaging agent uptake into the brain, or CSF assessment of t-tau amyloid beta 1-42</li> <li>• demonstrate objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the (WMS-IV LMII</li> <li>• have a MMSE score of 22 to 30 at screening and baseline.</li> </ul> <p><b>Questions for the clinical experts:</b></p> <p>What is the average wait time for patient who is a potential candidate for lecanemab to receive a PET scan or CSF assessment of t-tau amyloid beta [1-42] in Canada?</p> <p>At what point in the patient's course of disease will they typically be referred to a specialist in the treatment of AD?</p> <p>What is the average wait time for patient who is a potential candidate for lecanemab to see a specialist in the treatment of AD?</p> <p>MMSE is a proprietary test. How can MCI and mild AD dementia be defined using nonproprietary scoring systems (e.g., Montreal Cognitive Assessment, Global Deterioration Scale, and so forth [please outline any that are commonly used in clinical practice])?</p> | <p>Clinical experts reported substantial variability across Canadian provinces regarding access to and reimbursement for AD biomarker testing and specialist care. For example:</p> <ul style="list-style-type: none"> <li>• PET scan wait times range from 3 to 6 months in some provinces (e.g., Ontario, Quebec) to more than a year in others (e.g., Alberta), with additional constraints related to tracer availability and infrastructure.</li> <li>• CSF testing may have shorter turnaround times (about 1 month), but reimbursement barriers exist in some jurisdictions.</li> <li>• Access to specialists is generally limited, with wait times of 3 to 8 months or longer.</li> </ul> <p>The experts highlighted growing demand for timely access to disease-modifying therapies, necessitating health system reorganization and improved triage by primary care providers. They noted that interprofessional memory clinics may help mitigate specialist wait times, but additional education and appropriate compensation for primary care are needed to support effective triage.</p> <p>The clinical experts noted that measures of cognitive assessment commonly used clinical trial (WMS-IV LMII, MMSE) may not be routinely available at all centres in Canadian practice. However, there are alternative tools for measuring cognitive assessment in clinical practice across the provinces (e.g., MoCA, RUDAS, SLUMS, DCQ, TorCA). The experts clarified that diagnoses of MCI and dementia remain based on clinical evaluation, incorporating history, cognitive testing, and imaging.</p> |

| Implementation issues                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| <p><b>Other patient characteristics for eligibility (e.g., age restrictions, comorbidities)</b></p> <p>The following were inclusion criteria (related to patient characteristics) in the pivotal Clarity AD study:</p> <ul style="list-style-type: none"> <li>• age 50 to 90 years</li> <li>• BMI greater than 17 and less than 35.</li> </ul> <p><b>Question for the clinical experts:</b> Would you treat patients with lecanemab if they are outside of the aforementioned criteria (e.g., age &lt; 50 years or BMI &gt; 35)?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p>The clinical experts consulted by CDA-AMC reported that clinical judgment and informed discussion with patients should be adopted when deciding whether to treat individuals who fall outside the age and BMI criteria from the pivotal trial.</p> <p>CDEC acknowledged the clinical experts' input.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <p><b>Prior therapies required for eligibility</b></p> <p>The following were inclusion criteria (related to prior therapies) in the pivotal Clarity AD study:</p> <ul style="list-style-type: none"> <li>• If receiving approved AD treatment, (i.e., ChEIs or memantine, or both), the participant must have been taking a stable dose for at least 12 weeks. <ul style="list-style-type: none"> <li>◦ Note: In the Clarity AD trial, 52% and 53.5% of participants in the lecanemab and placebo groups, respectively, had current use of medication for symptoms of AD at the time of study initiation.</li> </ul> </li> <li>• Participants who had not previously been treated for AD could be entered into the study.</li> <li>• Unless otherwise stated, participants must have been taking stable doses of all other non-AD-related permitted concomitant medications for at least 4 weeks before baseline.</li> </ul> <p><b>Questions for the clinical experts:</b> Should patients treated with lecanemab also receive concomitant treatment with approved AD treatments (i.e., ChEIs or memantine, or both), unless there is a contraindication or intolerance? Would the answer change if the patient only had MCI?</p> | <p>All clinical experts consulted by CDA-AMC agreed that, at the present stage of evidence, they would not change their clinical practice in relation to AD symptomatic treatment. According to the experts, patients with early AD dementia may be treated with lecanemab and ChEIs or memantine, or both. Treatment with AD symptomatic therapy is not approved for the treatment of MCI in Canada.</p> <p>CDEC acknowledged the clinical experts' input.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p><b>Eligibility for retreatment</b></p> <p>In the Clarity AD study, participants who developed ARIA-E or ARIA-H that resulted in study drug interruption at any point permanently discontinued lecanemab if a third occurrence of either event met the criteria for study drug interruption or discontinuation.</p> <p><b>Questions for the clinical experts:</b> Should patients who develop ARIA-E or ARIA-H receive follow-up safety MRIs at 30, 60, and 90 days after identification (like in the Clarity AD study), or could fewer MRIs be satisfactory?</p> <p>Should patients who develop ARIA-E or ARIA-H receive a maximum of 3 opportunities to restart lecanemab if the ARIA resolves or does not worsen radiologically?</p> <p>Is APOE4 genotyping available in Canada?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p>The clinical experts consulted by CDA-AMC reported that follow-up MRI assessments after the occurrence of ARIA events should be context-specific to the individual patient. The decision to conduct additional assessments, with the intent to pause or discontinue treatment, should be based on clinical judgment of the treating physician and preferences of the patient. The experts stated that it is not feasible to establish a fixed number of restart possibilities.</p> <p>The clinical experts reported that, given the requirement of the determination of APOE4 allelic status for treatment eligibility, this testing will be completed for all patients as a companion diagnostic to lecanemab. In addition to eligibility, there is value in testing for counselling patients on ARIA risk based on APOE4 null vs. heterozygous status.</p> <p>The experts stated that APOE genotyping is currently available in Canada for other indications and this testing is not currently routinely conducted for patients with AD. Use as a companion diagnostic for lecanemab will be a new indication. This new indication should, however, be accompanied by a reimbursement</p> |

| Implementation issues                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <p>plan to ensure equitable access across Canada.</p> <p>CDEC acknowledged the clinical experts' input.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p><b>Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility</b></p> <p><b>Question for the clinical experts:</b> According to the sponsor's submission, it is likely that plaques start to develop before cognitive impairment. If a patient were discovered to have amyloid plaques on an image or CSF test but have no symptoms of cognitive impairment, should they be treated with lecanemab? Would the answer change if they had a strong family history of AD?</p>                                                                                                                                       | <p>The experts reported that patients who have demonstrated AD biomarker positivity, but are completely asymptomatic, would not be candidates for treatment with lecanemab. This would not change even if the patient had a positive family history of AD.</p> <p>CDEC acknowledged the clinical experts' input.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Considerations for continuation or renewal of therapy</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Challenges related to assessment and monitoring of therapeutic response</b></p> <p>Before initiating lecanemab therapy, patients must obtain a recent (within 6 months) baseline brain MRI to evaluate for pre-existing ARIA, then obtain an MRI before the third, fifth, seventh, and 14th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed (including an MRI, if indicated).</p> <p><b>Question for CDEC:</b> Should reimbursement of lecanemab be contingent on the clinician demonstrating that MRIs are available to the patient before the third, fifth, seventh, and 14th infusions?</p> | <p>The majority of experts felt that MRI availability should not be a condition for reimbursement of lecanemab. The experts believed that the treating physicians should establish and leverage partnerships with different imaging institutions to allow closer monitoring of individuals in the first 6 months of therapy (i.e., when the frequency of ARIA events is higher). The clinical experts expressed that MRI constraints must be addressed to allow for routine MRI monitoring of patients with AD who are receiving lecanemab, as is currently done for patients with other serious conditions. Some of the clinical experts noted that 10-minute MRI sequences would be used for monitoring for ARIA. Some of the clinical experts added that MRI availability is not a reimbursement requirement for other therapies or conditions.</p> <p>However, 1 clinical expert disagreed, stating that MRI monitoring requirements outlined in the product monograph must be followed and that MRI availability cannot be overlooked.</p> |
| <b>Considerations for discontinuation of therapy</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Definition of loss of response, absence of clinical benefit, or disease progression</b></p> <p>According to the product monograph, lecanemab should be discontinued once the patient progresses to moderate AD.</p> <p><b>Question for CDEC:</b> Should progress to moderate AD be a discontinuation condition for reimbursement?</p> <p><b>Question for clinical experts:</b> Are there any clinical scenarios where you would continue to treat a patient with lecanemab after they have progressed to moderate AD?</p>                                                                                                                               | <p>The clinical experts noted that discontinuation of lecanemab in cases of disease progression can be considered a general guideline, based on the current evidence. The experts noted that more evidence is needed regarding treatment maintenance and dosing continuations over time. The experts agreed that there is a need to involve patients and family members as part of the decision-making around when the drug gets discontinued. The experts felt that meaningful benefits may vary across different individuals and that there needs to be a discussion on treatment burden vs. benefits experienced by specific individuals. All of the clinical experts agreed that lecanemab should be discontinued if there is evidence of disease progression to a moderate or worse stage of dementia.</p> <p>CDEC acknowledged the clinical experts' input and commented that discontinuation of treatment with lecanemab is reasonable upon progression to moderate AD.</p>                                                              |
| <b>Considerations for prescribing of therapy</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Concerns related to accessing clinical specialists and/or special settings</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <p>The clinical experts suggested that initial prescribing of lecanemab be restricted to specialists (which could be done virtually). They</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

| Implementation issues                                                                                                                  | Response                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Question for CDEC:</b> Should lecanemab funding be restricted to specialists with access to MRIs, even in rural or remote settings? | noted that monitoring should also be performed by specialists, particularly during the first 6 months of treatment when the risk of ARIA is highest. The clinical experts commented that family physicians would be involved in screening patients and that family physicians with adequate training and supervision by the specialist may be able to reorder treatment in the patient's own community, with specialist support being available when needed. |

AD = Alzheimer disease; ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA with edema or effusion; ARIA-H = ARIA with microhemorrhage and hemosiderin deposit; BMI = body mass index; ChEI = cholinesterase inhibitor; CSF = cerebrospinal fluid; DCQ = Dépistage Cognitif de Québec; FDG = fluorodeoxyglucose; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; RUDAS = Rowland Universal Dementia Assessment Scale; SLUMS = Saint Louis University Mental Status Examination; TorCA = Toronto Cognitive Assessment; WMS-IV LMII = Wechsler Memory Scale IV-Logical Memory (subscale) II.

\*One of the clinical experts noted that FDG PET is not equivalent to amyloid PET (they are 2 different imaging techniques). Florbetaben is the nuclear medicine compound used to perform amyloid imaging, which quantifies amyloid burden in the brain, while FDG is the nuclear medicine compound used to perform FDG PET, which provides a metabolic profile of degenerative disease. FDG PET does not provide information on the underlying pathology in the brain, while amyloid imaging does.

## Clinical Evidence

### Systematic Review

#### Description of Studies

One phase III, double-blind, multicentre, randomized controlled trial (RCT), the Clarity AD trial, assessed the efficacy and safety of lecanemab compared to placebo in individuals with early AD (defined as MCI due to AD or mild dementia due to AD). Eligible adults were aged 50 to 90 years, with demonstrated evidence of amyloid positivity on PET or by CSF testing. The trial was conducted in 235 multinational sites, with 11 sites in Canada, from March 2019 to August 2022, and enrolled 1,795 participants. Participants were randomly assigned in a 1:1 ratio to receive either IV lecanemab (10 mg/kg) or placebo every 2 weeks.

The primary end point was the change from baseline in CDR-SB score at 18 months. The CDR-SB provides the sum score of 6 cognitive or functional domains, with a range of 0 to 18, with higher scores indicating a greater severity of impairment. Secondary outcomes included the change from baseline in ADAS-Cog14 score at 18 months and safety of lecanemab. ADAS-Cog14 scores range from 0 to 90, with higher scores indicating more severe impairment. HRQoL assessed using the QoL-AD outcome measure and caregiver burden measured by the ZBI were the exploratory outcomes in the Clarity AD trial. The QoL-AD total score ranges from 13 to 52, with higher scores indicating a better quality of life, and the ZBI total score ranges from 0 to 88, with a higher score indicating greater caregiver burden. The study was designed to evaluate prespecified end points in the overall trial population, which included patients of all APOE4 carrier types (i.e., APOE4 noncarriers, heterozygotes, and homozygotes). Because the indication under review is limited to patients who are APOE4 noncarriers and heterozygotes, the results of post hoc analyses for this population of patients (N = 1,521) for the end points of interest are presented in this Clinical Review report and have been reviewed by CDA-AMC.

In the indicated population of patients who were APOE4 noncarriers and heterozygotes, the mean age was approximately 71 years, and slightly more than half of the patients were female. The majority of participants

were white (> 75%) or Asian (approximately 16%). A greater proportion of patients had MCI due to AD (approximately 62%) than mild dementia due to AD (approximately 38%). Slightly more than 50% of patients were receiving AD symptomatic medication at baseline. In the indicated population from the Clarity AD trial, 37% were APOE4 noncarriers and 63% were APOE4 heterozygotes.

## Efficacy Results

### *CDR-SB Score*

In the indicated population (i.e., patients who were APOE4 noncarriers and heterozygotes), after 18 months, less cognitive and functional decline was reported for patients in the lecanemab group than in the placebo group. The adjusted mean change from baseline in CDR-SB score was 1.151 (standard error [SE] = 0.087) in the lecanemab group and 1.730 (SE = 0.085) in the placebo group, with an adjusted mean difference between groups of -0.579 (95% CI, -0.811 to -0.347;  $P < 0.00001$ ).

Subgroup analyses that were considered relevant to this review (clinical subgroup, symptomatic AD medication use, and age group) supported the primary analysis results favouring lecanemab over placebo on changes in CDR-SB score. However, the magnitude of the between-group difference varied among subgroups, and in patients younger than 65 years ( $n = 275$ ) the difference was -0.074 (95% CI, -0.544 to 0.395), with the CI crossing 0, indicating imprecision and uncertainty about the treatment benefit in this subgroup.

### *ADAS-Cog14 Score*

In the indicated population, at 18 months, the adjusted mean change from baseline in ADAS-Cog14 score was 4.211 (SE = 0.347) in the lecanemab group and 5.845 (SE = 0.342) in the placebo group, with an adjusted mean group difference of -1.633 (95% CI, -2.555 to -0.712;  $P = 0.00052$ ).

Subgroup analyses that were considered relevant to this review (as previously noted) supported the results favouring lecanemab over placebo on changes in ADAS-Cog14 score. However, the magnitude of the between-group difference varied among subgroups, and the CIs for several subgroups included 0, indicating imprecision and uncertainty of benefit.

### *QoL-AD Score*

In the indicated population, the adjusted mean change in QoL-AD score at 18 months (patient-reported) was -0.586 in the lecanemab group and -1.258 in the placebo group, with an adjusted between-group difference of 0.672 (95% CI, 0.209 to 1.136).

### *ZBI Score*

In the indicated population, the adjusted mean change from baseline to 18 months in ZBI score was 3.644 (SE = 0.433) in the lecanemab group and 5.925 (SE = 0.427) in the placebo group, with a between-group difference of -2.281 (95% CI, -3.389 to -1.173).

## Harms Results

In the indicated population, at 18 months, 88.1% of patients in the lecanemab group and 81.2% of patients in the placebo group had experienced at least 1 treatment-emergent adverse event (TEAE). At least 1 SAE,

excluding death, was experienced by 14.0% of patients in the lecanemab group and 10.3% of patients in the placebo group. Most SAEs required inpatient hospitalization or prolongation of existing hospitalization (lecanemab: 12.5%; placebo: 9.3%). Six deaths (0.8%) (unrelated to ARIA) occurred in the lecanemab group, and 7 deaths (0.9%) occurred in the placebo group. TEAEs leading to study drug dose adjustment were reported for 21.9% of patients in the lecanemab group and 10.1% of patients in the placebo group. In the lecanemab and placebo groups, respectively, 5.9% and 3.0% of patients had a TEAE leading to study drug withdrawal, 17.0% and 7.6% had a TEAE leading to a dose interruption, and 2.9% and 1.3% of patients had a TEAE leading to infusion interruption.

Notable harms (which included infusion-related reactions, ARIA-E events, and ARIA-H events) were reported in 39.0% of patients in the lecanemab group and 15.1% of patients in the placebo group. Infusion-related reactions occurred in 25.8% of patients in the lecanemab group and 7.1% of patients in the placebo group, and most were mild or moderate in severity (grade 1 or 2).

In the indicated population, ARIA events occurred more frequently in the lecanemab group than in the placebo group. The overall incidence of ARIA-E was 8.9% in the lecanemab group and 1.3% in the placebo group. Symptomatic ARIA-E events were reported in 12 patients (2%) in the lecanemab group and no patients in the placebo group. Serious ARIA-E events were reported in 4 patients (0.5%) in the lecanemab group and no patients in the placebo group. ARIA-H was observed in 12.9% of patients in the lecanemab group and 6.8% of patients in the placebo group. Symptomatic ARIA-H events were reported in 6 patients (0.8%) in the lecanemab group and 1 patient (0.1%) in the placebo group. Serious ARIA-H events were reported in 1 patient (0.1%) in the lecanemab group and no patients in the placebo group.

### Critical Appraisal

In the overall population of the Clarity AD trial, randomization and treatment allocation were appropriately performed and baseline characteristics between were balanced between the lecanemab and placebo groups. Baseline characteristics for the indicated population (i.e., APOE4 noncarriers and heterozygotes) were generally balanced across lecanemab and placebo groups. However, because the indicated population is a subset of the randomized trial population, imbalances in unmeasured confounders cannot be ruled out, which introduces a risk of bias and uncertainty in the internal validity. The study was double-blind and the investigators conducting medical management were independent from those conducting clinical assessments. Unblinding may have occurred among patients, caregivers, or investigators due to the occurrence of treatment-specific AEs (e.g., infusion-related reactions, ARIA). However, it could not be determined whether unblinding was an important source of bias in the Clarity AD study. Although concerns were identified by CDA-AMC regarding risk of bias, the certainty was not rated down, as it was unclear whether these limitations had a meaningful impact on the CDR-SB and ADAS-Cog14 outcome measures. The Clarity AD trial was designed to evaluate outcomes in the overall trial population and met its primary end point, with a statistically significant difference between groups in the mean change from baseline in CDR-SB score at 18 months. Multiplicity of testing key secondary end points, including ADAS-Cog14 scores, was planned and controlled by using a hierarchical testing procedure. Efficacy analyses for the indicated population (i.e., APOE4 noncarriers and heterozygotes) were not part of the original Clarity AD study design

and were performed post hoc. The planned primary end point and multiplicity control ensured that the main conclusions of the trial are statistically valid, serving as a robust foundation from which unplanned subgroup analyses can be cautiously interpreted. While it is acknowledged that the post hoc analyses performed for the indicated subpopulation were part of regulatory approval and not prespecified, they continue to carry a higher risk of false-positive findings despite the rigour of the original statistical analysis plan and primary end point results. This context helps frame the reliability and risk of bias of the findings for the indicated subpopulation within the broader trial evidence but does not mitigate their inherent post hoc nature. As previously noted, the certainty was not rated down for risk of bias for the CDR-SB and ADAS-Cog14 outcome measures.

In the indicated population, treatment withdrawals were generally balanced between the groups, with the proportions of individuals discontinuing study treatment due to AEs being slightly higher in lecanemab group (5.9%) than in the placebo group (3.0%). Sensitivity analyses conducted for CDR-SB score indicated robustness of the findings to missing data; however, it is unknown if the analysis for CDR-SB score was robust to plausible violations of the missing at random (MAR) assumption, as these analyses were not conducted for the indicated population. Sensitivity analyses conducted for the QoL-AD (patient-reported results) and ZBI indicated robustness of the findings to missing data.

Subgroup analyses were conducted on the subgroups of interest for this review in the indicated population. The findings suggested a greater treatment benefit (exceeding the 0.5-point threshold for meaningful benefit) of lecanemab versus placebo for the change in CDR-SB score at 18 months in patients aged 65 years or older, who had mild dementia due to AD, and who were receiving symptomatic AD medication at baseline. The observed benefit was smaller (less than 0.5 points) and less precise (CIs included 0, or no benefit) among patients not using symptomatic AD medication (−0.440 points;  $n = 588$ ), those with MCI due to AD (−0.402 points;  $n = 803$ ), and those younger than 65 years (−0.074 points;  $n = 249$ ). While not conclusive, the observed differences in the magnitude of the treatment effect among subgroups suggests that there is uncertainty in the treatment benefit and who is most likely to benefit from treatment with lecanemab.

Regarding external validity, the trial inclusion criteria are reflective of patients who would be candidates for lecanemab in clinical practice, according to the experts consulted by CDA-AMC, noting that the Health Canada conditionally approved indication is restricted by APOE4 carrier status, whereas patients of all APOE4 carrier types were eligible for the Clarity AD trial. Among the enrolled patients, there was underrepresentation of patients with racial or ethnic identities other than white, which may limit the generalizability of the study findings to practice in Canada. According to the clinical experts, there are disparities in amyloid PET access and variability in reimbursement of amyloid PET and CSF testing across jurisdictions in Canada, which are required for initiation of treatment. Because the Health Canada conditionally approved indication is only for patients who are APOE4 noncarriers and heterozygotes, testing for APOE4 carrier status is required. According to the clinical experts, assessment of APOE4 status is not currently routinely performed in clinical practice for patients with AD. *APOE* genotyping is already available in Canada for other medical indications, but lecanemab eligibility would represent a new indication and requires appropriate reimbursement. The clinical experts acknowledged the requirement for MRI monitoring for ARIA events and indicated that MRI capacity constraints exist in various provinces across the country, which may

pose challenges for treatment initiation and adequate monitoring; however, some clinical experts commented that a 10-minute MRI sequence can screen for ARIA, which could mitigate capacity constraints.

Regarding the clinical importance of the findings, validated between-group MIDs were not identified for the efficacy end points of the Clarity AD trial included in this review. For CDR-SB score, estimated MIDs for within-group changes were identified that ranged from 0.5 to 1.08 points (for patients with MCI), and from 1.63 to 2 points (for patients with mild dementia due to AD). According to the clinical experts, considering the large impact that any decline may have on patients with AD and their caregivers, a change in CDR-SB score of 0.5 points represents a clinically meaningful difference at the level of an individual patient with early AD. The clinical experts agreed that the 18-month duration of the Clarity AD trial was not sufficient for fully assessing the long-term efficacy and safety of lecanemab.

## **GRADE Summary of Findings and Certainty of the Evidence**

### ***Methods for Assessing the Certainty of the Evidence***

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform the CDA-AMC expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans (refer to the Outcomes section of this report for further explanation). The following list of outcomes was finalized in consultation with expert committee members:

- cognition and function (CDR-SB, ADAS-Cog14 scores)
- HRQoL (QoL-AD, ZBI scores)
- safety (SAEs, ARIA-E events, ARIA-H events).

Results of the ADCOMS, ADCS MCI-ADL, and EQ-5D-5L outcome measures are provided as supportive evidence in Appendix 1.

### ***Results of GRADE Assessments***

[Table 3](#) presents the GRADE summary of findings for lecanemab versus placebo.

**Table 3: Summary of Findings for Lecanemab vs. Placebo for Adults With Early AD<sup>a</sup> (APOE4 Noncarriers and Heterozygotes)**

| Outcome and follow-up                                                             | Patients (studies), N | Relative effect (95% CI)                                                                                                 | Absolute effects (95% CI) |                    |                           | Certainty               | What happens                                                                                                             |
|-----------------------------------------------------------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------|--------------------|---------------------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------|
|                                                                                   |                       |                                                                                                                          | Placebo                   | Lecanemab          | Difference                |                         |                                                                                                                          |
| Cognition and function                                                            |                       |                                                                                                                          |                           |                    |                           |                         |                                                                                                                          |
| CFB in CDR-SB (0 [best] to 18 [worst])<br>Follow-up: 18 months                    | 1,466 (1 RCT)         | NA                                                                                                                       | 1.730                     | 1.151 (95% CI NR)  | -0.579 (-0.811 to -0.347) | Moderate <sup>b,c</sup> | Lecanemab likely results in less decline in cognition and function as measured by the CDR-SB when compared with placebo. |
| CFB in ADAS-Cog14 (0 [best] to 90 [worst])<br>Follow-up: 18 months                | 1,459 (1 RCT)         | NA                                                                                                                       | 5.845                     | 4.211 (95% CI NR)  | -1.633 (-2.555 to -0.712) | Moderate <sup>c,d</sup> | Lecanemab likely results in less decline in cognition as measured by the ADAS-Cog14 when compared with placebo.          |
| HRQoL                                                                             |                       |                                                                                                                          |                           |                    |                           |                         |                                                                                                                          |
| CFB in QoL-AD: Patient-reported (13 [worst] to 52 [best])<br>Follow-up: 18 months | 1,239 (1 RCT)         | NA                                                                                                                       | -1.258                    | -0.586 (95% CI NR) | 0.672 (0.209 to 1.136)    | Moderate <sup>e</sup>   | Lecanemab likely results in less decline in HRQoL as measured by the QoL-AD when compared with placebo.                  |
| CFB in ZBI (0 [best] to 88 [worst])<br>Follow-up: 18 months                       | 1,238 (1 RCT)         | NA                                                                                                                       | 5.925                     | 3.644 (95% CI NR)  | -2.281 (-3.389 to -1.173) | Low <sup>e,f</sup>      | Lecanemab may result in less worsening of caregiver burden as measured by the ZBI when compared with placebo.            |
| Harms                                                                             |                       |                                                                                                                          |                           |                    |                           |                         |                                                                                                                          |
| SAEs (not including death)<br>Follow-up: 18 months                                | 1,521 (1 RCT)         | At least 1 SAE was reported in 106 patients (14.0%) in the lecanemab group and 79 patients (10.3%) in the placebo group. |                           |                    | 3.7 (0.4 to 6.9)          | Moderate <sup>g</sup>   | Lecanemab likely results in a higher frequency of SAEs when compared with placebo.                                       |
| ARIA-E<br>Follow-up: 18 months                                                    | 1,521 (1 RCT)         | ARIA-E events were reported in 67 (8.9%) patients in the lecanemab group and 10 (1.3%) patients in the placebo group.    |                           |                    | 7.5 (5.4 to 9.7)          | Moderate <sup>g</sup>   | Lecanemab likely results in a higher frequency of ARIA-E events when compared with placebo.                              |

| Outcome and follow-up          | Patients (studies), N | Relative effect (95% CI)                                                                                                                                          | Absolute effects (95% CI) |           |                  | Certainty             | What happens                                                                                |
|--------------------------------|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-----------|------------------|-----------------------|---------------------------------------------------------------------------------------------|
|                                |                       |                                                                                                                                                                   | Placebo                   | Lecanemab | Difference       |                       |                                                                                             |
| ARIA-H<br>Follow-up: 18 months | 1,521 (1 RCT)         | ARIA-H events (microhemorrhage or superficial siderosis) were reported in 98 (12.9%) patients in the lecanemab group and 52 (6.8%) patients in the placebo group. |                           |           | 6.1 (3.2 to 9.1) | Moderate <sup>g</sup> | Lecanemab likely results in a higher frequency of ARIA-H events when compared with placebo. |

AD = Alzheimer disease; ADAS-Cog14 = Alzheimer's Disease Assessment Scale – 14-Item Cognitive Subscale; ARIA = amyloid-related imaging abnormality; ARIA-E = ARIA with edema or effusion; ARIA-H = ARIA with microhemorrhage and hemosiderin deposit; CDA-AMC = Canada's Drug Agency; CDR-SB = Clinical Dementia Rating – Sum of Boxes; CFB = change from baseline; CI = confidence interval; HRQoL = health-related quality of life; MAR = missing at random; MCI = mild cognitive impairment; MID = minimal important difference; NA = not applicable; NR = not reported; QoL-AD = Quality of Life in Alzheimer's Disease; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus; ZBI = Zarit Burden Interview.

Notes: Study limitations (which refer to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. The subgroup analyses were not adjusted for multiple statistical comparisons, statistical tests of interaction were not reported to be able to confirm whether treatment effects differed among subgroups, and sample sizes were relatively small for certain subgroups (e.g., those younger than 65 years). Additional limitations exist regarding the certainty of subgroup analyses for the indicated population, which itself is a subgroup of the overall trial population.

<sup>a</sup>Early AD refers to MCI due to AD or mild dementia due to AD.

<sup>b</sup>Rated down 1 level for serious concerns about imprecision. No published between-group MID was identified. The within-group MID has been estimated to range from 0.5 to 2 points (0.5 to 1.08 points for MCI, 1.63 to 2 points for mild dementia due to AD). Clinical experts consulted by CDA-AMC suggested that, even though a change in CDR-SB score of 0.5 points represents a clinically meaningful difference at the level of an individual patient with early AD, the value is appropriate to use for judging the clinical relevance of the difference between groups; therefore, the 0.5 value was used as the threshold. Rated down 1 level for serious imprecision because 1 end (–0.347) of the 95% CI for the between-group difference indicated the possibility of trivial benefit. Not rated down for inconsistency despite some subgroup results showing differences in the magnitude of treatment benefit, because the study was not designed for inferences in the subgroups and no statistical tests for interaction were conducted.

<sup>c</sup>Not rated down for serious risk of bias. Although concerns were identified (e.g., randomization potentially not preserved in the results for the indicated population, and the potential unblinding of patients, their caregivers, and study personnel), the certainty was not rated down as it was unclear whether these limitations had a meaningful impact on the outcome measure.

<sup>d</sup>Rated down 1 level for serious concerns about imprecision. No published between- or within-group MID was identified and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Rated down 1 level for serious imprecision because although a between-group difference suggests benefit of lecanemab compared to placebo, the clinical significance is uncertain relative to the null effect as the target of certainty. Not rated down for inconsistency despite some subgroup results showing differences in the magnitude of treatment benefit, because the study was not designed for inferences in the subgroups and no statistical tests for interaction were conducted.

<sup>e</sup>Rated down 1 level for serious imprecision. No published between- or within-group MID was identified and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Rated down because although a between-group difference suggests benefit of lecanemab compared to placebo, the clinical significance is uncertain relative to the null effect as the target of certainty.

<sup>f</sup>Rated down 1 level for serious indirectness. The ZBI instrument was not developed and validated for caregiver burden in early AD, limiting applicability.

<sup>g</sup>Rated down 1 level for serious imprecision. There was no known threshold for a clinically important effect and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Rated down because the clinical significance is uncertain relative to the null effect as the target of certainty.

Sources: Details included in the table are from the sponsor's Summary of Clinical Evidence on Adult Patients who are APOE4 Noncarriers and Heterozygotes, sponsor's data on file, and sponsor's response to the CDA-AMC request for additional information.

## Long-Term Extension Studies

### Description of Studies

Preliminary results from 1 ongoing, long-term, single-arm, OLE study, the Clarity AD OLE study, provided evidence regarding the longer-term efficacy, safety, and tolerability of lecanemab in adults with early AD (MCI due to AD or mild dementia due to AD). Participants who completed the Clarity AD core study were enrolled in the OLE and received lecanemab 10 mg/kg biweekly regardless of initial allocation in the core study (i.e., lecanemab or placebo) for at least 6 months, with treatment to be continued for up to 48 months.

The Clarity AD OLE primary outcomes included change in CDR-SB score from the Clarity AD core study baseline and incidence of AEs. Several exploratory outcomes were specified, including change from the Clarity AD core study baseline in ADAS-Cog14, QoL-AD, and ZBI scores. As with the core study, the Clarity AD OLE study was designed to evaluate prespecified end points in the overall trial population (N = 1,390), which comprised patients of all APOE4 carrier types (i.e., APOE4 noncarriers, heterozygotes, and homozygotes). Because the indication under review is limited to patients who are APOE4 noncarriers and heterozygotes, the results of post hoc analyses for this population of patients (N = 1,187) for the end points of interest are presented in this Clinical Review report.

For the indicated population of patients who were APOE4 noncarriers and heterozygotes, most of the participants who entered the extension phase were from North America (59%) and were white (77%). The mean age of participants was 72 years, with approximately 49% of patients being male. Patients who had MCI due to AD comprised 63% of enrolled participants and the remaining 37% of patients had had mild dementia due to AD. Among the indicated population, 36% of patients were APOE4 noncarriers and 64% were APOE4 heterozygotes. More than half (55%) of patients were receiving symptomatic medication for AD.

### Efficacy Results

Preliminary efficacy results were available for up to 36 months of follow-up (18 months for the Clarity AD core study plus 18 months for the Clarity AD OLE study). Efficacy comparisons for CDR-SB score were made between participants in the OLE study who received lecanemab in the core study (and continued treatment in the extension phase) and an external observational cohort (from the ADNI study). Data for the CDR-SB outcome at 48 months are also reported, as submitted by the sponsor in their request for reconsideration.

#### *CDR-SB Score*

For the indicated population (i.e., APOE4 noncarriers and heterozygotes), for the adjusted mean change in CDR-SB score from the core study baseline, less decline in CDR-SB score was observed for the OLE group compared to the ADNI cohort, with a between-group difference of -0.774 (95% CI not reported [NR]) at 36 months.

As submitted in the sponsor's request for reconsideration, the difference in the adjusted mean change from baseline in CDR-SB score between patients who continued lecanemab treatment from the core study and the external ADNI cohort was -1.308 (95% CI, -2.166 to -0.450) at 48 months.

### **ADAS-Cog14 Score**

For the indicated population, the adjusted mean change from baseline in ADAS-Cog14 score at 36 months was 10.821 (SE = 0.591) in the early-start group (i.e., those who received lecanemab in the core study) and 12.083 (SE = 0.587) in the delayed-start group (i.e., those who received placebo in the core study), representing a between-group difference of -1.262 (95% CI, -2.876 to 0.353).

### **QoL-AD Score**

For the indicated population, at 36 months, the adjusted mean change from baseline in the QoL-AD patient survey score was -1.258 (SE = 0.256) in the early-start group and -1.705 (SE = 0.258) in the delayed-start group, with an adjusted mean between-group difference of 0.447 (95% CI, -0.245 to 1.138).

### **ZBI Score**

For the indicated population, the adjusted mean change from baseline in ZBI score at 36 months was 6.515 (SE = 0.555) in the early-start group and 8.083 (SE = 0.556) in the delayed-start group, with an adjusted mean between-group difference of -1.568 (95% CI, -3.047 to -0.089).

### **Harms Results**

For the indicated population, at 36 months, at least 1 TEAE was reported for 90.6% of patients, with serious TEAEs reported for 20.4% of patients. TEAEs leading to study drug withdrawal were reported in 8.2% of patients. TEAEs of special interest (ARIA-E, ARIA-H, macrohemorrhage, infusion-related reactions, skin rash, other hypersensitivity, suicidal ideation, and suicidal behaviour) were reported for 42.7% of participants. Nineteen deaths were reported; 6 occurred in the core study with lecanemab treatment and 13 occurred in the extension phase. The frequency of ARIA-E overall was 10.7% and the frequency of symptomatic ARIA-E was 2.0%. Overall ARIA-H and symptomatic ARIA-H were reported in 19.3% and 1.4% of patients, respectively. The frequency of macrohemorrhage was 0.5%.

In the sponsor's request for reconsideration, harms data at 48 months (18 months from the core study plus 30 months from the OLE) were submitted. For the indicated population, 91.5% of patients had at least 1 TEAE. Serious TEAEs (including death) were reported in 22.6% of patients. There were 23 treatment-emergent deaths reported (1.7%), of which 6 deaths occurred in the core study with lecanemab treatment (none deemed by the sponsor to be related to study drug), and 17 additional deaths occurred in the OLE (3 possibly related to study treatment, according to the sponsor). Serious TEAEs (not including death) were reported in 20.9% of patients. TEAEs leading to study drug dose interruption and study drug withdrawal were reported for 25.6% and 9.2% of patients, respectively. TEAEs of special interest were reported for 44.4% of patients. ARIA-E occurred in 11.1% of patients and ARIA-H occurred in 21.4% of patients. The frequency of macrohemorrhage was 0.5%.

### **Critical Appraisal**

For the assessment of comparative efficacy and harms, the lack of a direct randomized control group is a key limitation of the Clarity AD OLE trial. The absence of an internal comparator makes the changes observed difficult to attribute to lecanemab versus the natural history of the disease. To overcome issues related to the lack of an internal control group, the analysis compared the change in CDR-SB score from

the Clarity AD core study baseline to modelled natural disease progression using an external observational ADNI cohort. This analysis was not described in the Clarity AD OLE study protocol or statistical analysis plan provided by the sponsor; therefore, it was unclear if this analysis was prespecified. Additional information submitted by the sponsor stated that the a priori matched observational cohort from the ADNI study was created during the design of the Clarity AD study to aid in decision-making for the protocol design and before database lock. Limited information regarding the ADNI cohort was provided, as well as limited information on matching methodology, statistical procedures, and success of matching. Few baseline characteristics were reported between the trial and the ADNI cohort. An imbalance between the Clarity AD core study group and ADNI cohort in baseline CDR-SB score was noted, suggesting a risk of bias in the comparison; however, it is not clear if the direction of bias would be in favour of or against lecanemab. Additionally, although CDR-SB score was measured as an ADNI study outcome, based on the information provided, the metric reported was rate of decline rather than change from baseline at fixed time points as in the Clarity AD trial. Therefore, values would need to be estimated at time points to make the data comparable. Data quality information for the ADNI study was not available. Therefore, these factors reduce the validity of the comparison between the ADNI cohort and the OLE participants, and its ability to inform the long-term treatment effect. Results for the change in CDR-SB score were mainly descriptive, without corresponding CIs, despite between-group comparisons with the ADNI cohort being conducted.

Some of the clinical experts consulted by CDA-AMC expressed the opinion that the ADNI study is a well-known natural history study and that the ADNI cohort was the best available external comparator. They also noted that the ADNI cohort was composed of patients who were less likely to experience significant deterioration or develop behavioural symptoms, and because of this, the difference observed between the ADNI and OLE groups was likely underestimated.

Enrolment in the Clarity AD OLE study required that patients complete the Clarity AD core study (patients who discontinued the core study were excluded from the extension phase). Patients who chose to enrol in the extension study may have been those from the core study treatment arm who had a more favourable response and/or better tolerability to lecanemab, or patients in the core study with better adherence to their assigned treatment. Conversely, it is possible that some patients who completed the core study opted to enrol in the subcutaneous lecanemab substudy rather than participate in the Clarity AD OLE study (which used IV administration). By the 36-month data cut-off, 24.7% of patients had discontinued study treatment, raising concerns about attrition bias and increasing the potential impact of any selection bias on the results.

Given that patients in the Clarity AD OLE trial originally participated in the Clarity AD core study, and eligibility criteria were aligned between the 2 phases, generalizability advantages and limitations noted for the core study would be expected to be relevant to the long-term extension phase. The population in the OLE likely represents a more select population compared with the core study, representing those who may experience better outcomes than the broader population in Canada, as previously noted.

For the outcome of change in CDR-SB score at 36 months from the core study baseline as compared to the external ADNI cohort, the generalizability of the preliminary efficacy results is uncertain, given that limited information pertaining to the sample of patients used as an external control has been provided by

the sponsor. Some of the clinical experts stated that the decline in CDR-SB score observed in the ADNI cohort was aligned with what would be expected in clinical practice for patients with early AD who are not receiving a disease-modifying therapy. Other clinical experts stated that decline is likely slower than what would occur in clinical practice, given that patients who remain in longitudinal, observational studies tend to be those with the slowest disease progression. As previously mentioned, some clinical experts emphasized that the ADNI cohort was the best available external comparator and that the difference observed was likely underestimated.

The Clarity AD OLE study is expected to continue for up to 48 months (in addition to the 18-month core trial). For this review, preliminary results were available at 36 months (18 months from the core study plus 18 months from the OLE study), with some additional results at 48 months (18 months from the core study plus 30 months from the OLE study) provided by the sponsor in their request for reconsideration. The availability of only preliminary efficacy and safety information is a limitation in evaluating the long-term effects of lecanemab.

In their request for reconsideration, the sponsor submitted additional data and information pertaining to the methods of the Clarity AD OLE and ADNI matching and analyses. Following review of this information, the CDA-AMC review team still had concerns regarding the matching methodology and success of matching, attrition and handling of missing data, statistical procedures, and potential for selective analytic decisions. Consistent with the previously noted critical appraisal, these factors reduced the validity of the comparison between the ADNI cohort and the OLE participants, and its ability to inform the long-term treatment effect.

## Indirect Comparisons

There were no indirect treatment comparisons included in this submission.

## Studies Addressing Gaps in the Evidence From the Systematic Review

The sponsor submitted results of a single study to address gaps in the systematic review evidence (Clarity AD and Clarity AD OLE results) regarding uncertainty in lecanemab treatment duration and discontinuation of lecanemab in actual clinical practice. The study examined a period (referred to as the *gap period*) that occurred between the 2 phases of a phase 2b study with an OLE, during which patients stopped receiving lecanemab. Participants had early AD and included all APOE4 carrier types (i.e., APOE4 noncarriers, heterozygotes, and homozygotes). It was reported that, during the gap period, the rates in clinical progression based on CDR-SB scores were similar for both the original lecanemab and placebo groups, and brain amyloid reaccumulation was observed in patients previously treated with lecanemab. Based on the findings of this study, the sponsor suggested that continued suppression of the rate of disease progression may depend on continued lecanemab treatment.

The gap period analysis does not seem to have been conceived as confirmatory, which limited the interpretation of cognitive outcomes observed during the gap period.

Some of the clinical experts consulted by CDA-AMC identified issues regarding the use of lecanemab in clinical practice that have not been addressed by the Clarity AD core study, including longer-term effects on

cognition and function and long-term AEs. However, the sponsor submitted longer-term evidence from the Clarity AD OLE study, up to 36 months (18 months from the Clarity AD core study plus 18 months from the Clarity AD OLE study), as previously described. Another issue not addressed by the Clarity AD core study noted by some clinical experts was the clinical importance and impact of the occurrence and severity of ARIA-E and ARIA-H. It was also noted that the importance of observed variation in treatment effect among various subgroups of patients on CDR-SB results needs further research. Evidence on when to discontinue lecanemab, especially for lack of efficacy, was noted as an uncertainty not addressed by the Clarity AD trial; however, the clinical experts agreed that treatment should be discontinued upon disease progression to a moderate or worse stage of dementia.

Some of the clinical experts emphasized that, as a single clinical trial, the Clarity AD trial should not be expected to address the aforementioned issues, and that the long-term extension study, postmarket evaluations, and real-world experience will help to evaluate longer-term outcomes.

CDA-AMC indicated that the evidence gaps from the Clarity AD trial that were identified by CDA-AMC in consultation with clinical experts were not addressed.

## Testing Procedure Assessment

*APOE* genotype testing most commonly identifies the combination of the 3 most prevalent *APOE* alleles (i.e., epsilon 2, epsilon 3, and epsilon 4) an individual carries. Lecanemab is indicated specifically for adults who are *APOE*4 noncarriers or heterozygotes as outlined by the product monograph. Individuals with *APOE*4 alleles have been reported to be at a greater risk for ARIA compared to those who do not carry them, with *APOE*4 homozygotes having the greatest risk, followed by *APOE*4 heterozygotes. Various analytical approaches can be used to determine *APOE* allelic carrier status and include DNA-based and protein-based testing methods. *APOE* genotype testing should be performed after AD biomarker testing, and only in those who may be eligible for and are interested in anti-amyloid beta treatment.

Key considerations and relevant information available from materials submitted by the sponsor, input from the clinical experts, and sources from the literature were validated by the review team when possible and are summarized in [Table 4](#).

**Table 4: Considerations for *APOE*4 Carrier Status Testing**

| Consideration          | Criterion                                                                     | Available information                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Health systems–related | Number of individuals in Canada expected to require the test (e.g., per year) | According to the sponsors, the expected number of individuals who would require <i>APOE</i> 4 genotype testing would align with the estimated number of individuals with MCI and mild dementia who have an AD biomarker-confirmed diagnosis. The sponsor estimates that the number of new individuals expected to receive <i>APOE</i> 4 genotype testing would be 2,227 in year 1, 6,240 in year 2, and 17,490 in year 3. |

| Consideration   | Criterion                                                                                     | Available information                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                 | Availability and reimbursement status of the testing procedure in jurisdictions across Canada | One clinical expert indicated that <i>APOE</i> genotype testing using PCR is currently used for ARIA risk assessment associated with amyloid-targeted treatment for AD in British Columbia. Otherwise, <i>APOE</i> genotype testing is currently available for the diagnosis of a specific type of dyslipidemia in several provinces.                                                                                                                                                                                                                                                                          |
|                 | Testing procedure as part of routine care                                                     | <i>APOE</i> genotype testing is not currently performed as part of routine testing for early AD in Canada.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                 | Repeat testing requirements                                                                   | Repeat testing for <i>APOE</i> genotyping is not required once <i>APOE4</i> carrier status is determined for those who may be eligible for lecanemab.                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                 | Impacts on human and other health care resources by provision of the testing procedure        | The clinical experts noted that there would be an expected increase each year in <i>APOE4</i> genotype testing associated with the diagnostic workup to determine treatment eligibility if lecanemab were to be funded; however, testing infrastructure for <i>APOE</i> genotype testing is already established and introducing additional “medically necessary” indications would be feasible. Additionally, the clinical experts do not anticipate that this broadening of scope would substantially impact human and other health care resources due to the targeted nature and staged approach of testing. |
| Patient-related | Accessibility of the testing procedure in jurisdictions across Canada                         | Access to testing is limited and is only recommended for ARIA risk assessment associated with amyloid-target treatment in people living with confirmed early AD.                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                 | Expected turnaround times for the testing procedure                                           | The current expected turnaround times for <i>APOE</i> genotype testing in Canada ranges from 10 business days (for private testing platforms) up to 4 weeks (for standard, publicly available <i>APOE</i> genotype testing platforms). The clinical experts noted that the expected turnaround times would not likely impact timely access to treatment.                                                                                                                                                                                                                                                       |
|                 | Burden associated with the testing procedure for patients, families, and/or caregivers        | Individuals may experience adverse emotional or mental stress when learning the results of the test and people who are <i>APOE4</i> homozygotes guarantee that their biological children will also be <i>APOE4</i> carriers. <i>APOE4</i> genotype testing can have a significant effect on emotional well-being, lifestyle choices, future planning, personal health insurance implications, and therapeutic decision-making for people living with early AD, their family members, and caregivers.                                                                                                           |
| Clinical        | Diagnostic test accuracy and clinical validity of the testing procedure                       | <i>APOE</i> genotype testing within the context of AD risk assessment for anti-amyloid beta treatment is targeted for identifying the presence of the epsilon 4 allele; thus, published evidence reports that DNA-based testing methods for determining <i>APOE4</i> carrier status have a high diagnostic accuracy.                                                                                                                                                                                                                                                                                           |
|                 | Risks of harm associated with the testing procedure                                           | <i>APOE</i> genotype testing methods can be performed safely, but some individuals may experience discomfort during bloodwork. No other significant risks of harm are associated with <i>APOE</i> genotype testing.                                                                                                                                                                                                                                                                                                                                                                                            |
| Cost            | Projected cost of the testing procedure                                                       | According to sponsor-submitted information and clinical expert input, <i>APOE</i> genotype testing may be purchased out-of-pocket. The out-of-pocket costs for <i>APOE</i> genotype testing are approximately \$100 from a public laboratory and range from \$175 to \$990 for private laboratories, depending on the testing method used.                                                                                                                                                                                                                                                                     |

AD = Alzheimer disease; ARIA = amyloid-related imaging abnormality; MCI = mild cognitive impairment; PCR = polymerase chain reaction.

## Ethical Considerations

Ethical considerations were identified by reviewing relevant literature as well as patient group, clinician group, clinical expert, and drug program input gathered during this review.

The ethical considerations identified in this review include those related to the following:

- Diagnosis, treatment, and experiences of AD:** AD is a progressive neurodegenerative disorder and the most common form of dementia. Several groups — including women, Indigenous Peoples, and racialized groups — are disproportionately impacted by AD, due to biological factors as well as structural barriers to diagnosis and care. AD negatively impacts quality of life for both patients and caregivers, as AD causes memory loss, anxiety, depression, behavioural changes, and disorientation, and requires increasing caregiver support as the disease progresses. There are several systems-level gaps in AD care and management in Canada, including barriers to diagnosis of AD due to wait times for primary care, and access to specialists and diagnostic resources; these gaps tend to be inequitably distributed across population groups and are exacerbated for those in rural or remote areas, and those in racialized and other equity-deserving groups. Patients and clinicians reported an unmet need for treatment that slows or reverses disease progression and improves or maintains cognition, function, and quality of life. Standard of care treatments are for dementia due to AD but not MCI due to AD; these medications may reduce symptom severity but do not slow, stop, or reverse the disease.
- Evidence used in the evaluation of lecanemab:** Clinical trial evidence had limited representation of groups disproportionately impacted by AD, yielding uncertainties in the implications of results across diverse populations, which could potentially perpetuate or exacerbate existing inequities. Further, long-term evidence on the safety and efficacy of lecanemab, beyond the data appraised in this review is unknown, and there are no comparative data relative to relevant comparators in the Canadian context, complicating decision-making for patients and caregivers, providers, and health systems.
- Clinical use and implementation of lecanemab:** Treatment with lecanemab is more resource-intensive than the existing standard of care and treatment pathway, requiring access to specialists, diagnostic infrastructures, infusion clinics, and MRIs for monitoring. These resources are in short supply in the Canadian context, raising concerns about inequities and access limitations, as well as the ability to safely administer and monitor the drug. Prescribing decisions for the population of AD patients who qualify for treatment with lecanemab will require shared decision-making in light of uncertain benefit; known risks; and challenges with access, administration, and monitoring in a resource-constrained health system. This can be supported by robust informed-consent conversations with patients and their families, taking into account heightened public and patient expectations for disease-modifying therapies for AD.
- Health systems:** The introduction of anti-amyloid antibody therapies, including lecanemab, is expected to require expanding systems capacity as well as reorganizing health systems in Canada to accommodate timely diagnosis and inform decisions about appropriate patient selection, safe use,

and ensure equitable access. The costs of funding lecanemab and supporting infrastructures raise concerns about health system sustainability, resource allocation, and priority setting.

## Economic Evidence

### Cost and Cost-Effectiveness

**Table 5: Summary of Economic Evaluation**

| Component                          | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Type of economic evaluation</b> | Cost-utility analysis<br>Markov model                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Target population</b>           | Adults with early Alzheimer disease (mild cognitive impairment or mild dementia stage of disease) who are APOE4 noncarriers or heterozygotes, with confirmed amyloid beta pathology                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Treatment</b>                   | Lecanemab plus standard of care                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Dose regimen</b>                | 10 mg/kg once every 2 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Submitted price</b>             | \$370.80 per 2 mL single-dose vial<br>\$927.00 per 5 mL single-dose vial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Submitted treatment cost</b>    | \$29,874.59 per year, based on a patient weight of 65.58 kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Comparator</b>                  | Standard of care including donepezil, rivastigmine, galantamine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Perspective</b>                 | Publicly funded health care payer<br>Societal perspective                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Outcomes</b>                    | QALYs, LYs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Time horizon</b>                | Lifetime (30 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Key data sources</b>            | Clarity AD trial<br>Real-world evidence (Potashman et al., 2021; Knapp et al., 2016; and Crowell et al., 2023)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Key limitations</b>             | <ul style="list-style-type: none"> <li>• The sponsor assumed that the treatment benefit of lecanemab is not contingent on remaining on treatment, meaning a patient who receives 1 cycle of lecanemab and discontinues treatment has the same benefit as a patient who remains on treatment indefinitely. This assumption conflicts with evidence presented for this review that shows treatment benefit stops after discontinuation. This assumption overestimates the benefit of lecanemab for those who discontinue.</li> <li>• The sponsor underestimated the drug acquisition and administration costs associated with lecanemab by assuming perfect vial sharing, underestimating the mean patient weight, and excluding administration costs. However, the sponsor noted that a patient support program will be available to health care providers and their patients who decide to enrol in the program. If this program is provided and adopted by health care providers, then administration costs may not be incurred.</li> <li>• The sponsor assumed some patients may regress through AD health states, meaning a patient can go from severe AD to mild cognitive impairment. As AD is a progressive disease, clinical experts noted that this was not clinically valid.</li> <li>• The impact of lecanemab on mortality is uncertain. No evidence on mortality impact could</li> </ul> |

| Component                         | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   | <p>be derived from the trial. In discussion with clinical experts, mortality benefits were seen as plausible if disease progression were delayed. In the evidence provided by the sponsor, mortality was shown to be heterogenous among different patients, especially when age was considered. This was not considered in the model, making any life extension benefit uncertain.</p> <ul style="list-style-type: none"> <li>• The sponsor assumed that life extension with lecanemab would remove all caregiver burden. This assumption was not based on evidence and effectively doubled the benefit of any life extension that occurred.</li> <li>• The loss of caregiver productivity in the sponsor's model was uncertain, and did not account for the additional time caregivers would spend accompanying patients to biweekly IV infusions, monitoring, and safety appointments associated with lecanemab.</li> <li>• Diagnostic testing costs were not fully accounted for in the sponsor's economic model.</li> </ul> |
| <b>CDA-AMC reanalysis results</b> | <ul style="list-style-type: none"> <li>• CDA-AMC addressed key limitations with respect to the treatment benefit of lecanemab after discontinuation, incorporation of caregiver utilities, cost of lecanemab administration, caregiver productivity loss, transitions between disease severity–based health states, and diagnostic testing. Results from the CDA-AMC reanalysis were as follows:</li> <li>• Publicly funded health care payer perspective: ICER = \$288,760 per QALY gained (incremental costs: \$129,298; incremental QALYs: 0.45)</li> <li>• Societal perspective: ICER = \$265,505 per QALY gained (incremental costs: \$125,920; incremental QALYs: 0.47)</li> </ul>                                                                                                                                                                                                                                                                                                                                        |

AD = Alzheimer disease; ICER = incremental cost-effectiveness ratio; LY= life-year; QALY = quality-adjusted life-year.

## Budget Impact

CDA-AMC identified the following limitations in the sponsor's base case: uncertainty in the sponsor's estimated eligible population, uncertainty in the sponsor's approach to calculating the budget impact, and uncertainty in the public drug plan beneficiaries. Based on the CDA-AMC base case, the estimated incremental budget impact of funding lecanemab for adults with mild AD who are APOE4 noncarriers or heterozygotes was \$66,855,380 in year 1, \$175,738,005 in year 2, and \$485,830,484 in year 3. Therefore, the 3-year incremental budget impact was \$728,423,869. The budget impact is sensitive to the number of patients eligible for treatment with lecanemab, which may be related to public drug plan coverage and capacity constraints that limit the identification of eligible patients. In the long term, capacity constraints in Canada are uncertain as the treatment landscape for AD evolves.

## Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for lecanemab for the treatment of patients with a clinical diagnosis of MCI or mild dementia due to AD (early AD) who are APOE4 noncarriers or heterozygotes, and who have confirmed amyloid pathology. In their request, the sponsor identified the following issues:

- The sponsor stated that there should be consideration of the full scope of unmet need in early AD and that the unmet need assessment should reflect the full deliberative framework. The sponsor requested that CDEC acknowledge that early AD is a chronic, progressive, debilitating, and ultimately fatal disease for which there are no therapies to slow the progression, underscoring the critical need for effective treatments that are initiated early in the disease course. The sponsor requested that

factors identified as important to both patient groups and clinician groups be expressly weighed in judging unmet need; namely, disease severity and delaying progression, functional decline and loss of independence, caregiver burden and HRQoL, and risk of institutionalization, alongside tolerability and access.

- The sponsor stated that the draft recommendation focused on mean CDR-SB and ADAS-Cog14 scores and did not consider the totality of the submitted evidence. The sponsor requested that the clinical benefit of lecanemab be assessed in the context of the totality of evidence, including additional outcomes that are clinically relevant to patients (ADCS MCI-ADL, time-to-worsening, and rate-of-change analyses). The sponsor also submitted the results of a progressor analysis based on the CDR-SB that they requested be considered.
- The sponsor stated that reassessment is needed for the Clarity AD OLE and ADNI analysis and long-term benefit of lecanemab. The sponsor requested that CDEC consider methodological clarifications regarding the comparison and longer-term 48-month results of the Clarity AD OLE trial.
- The sponsor stated that the committee's conclusion of uncertain clinical meaningfulness in the CDR-SB results rests on misapplication of the MID, imprecision, and subgroup assumptions that do not reflect the totality of evidence. The sponsor requested that CDEC align its interpretation of the CDR-SB effect size in the Clarity AD trial with the conclusions of the CDA-AMC Clinical Review and clinical experts.
- The sponsor stated that downgrading of the certainty in the evidence for inconsistency applied to CDR-SB and ADAS-Cog14 scores based on subgroup effects was inappropriate based on core GRADE methodology, and requested that this be reconsidered.
- The sponsor stated that real-world evidence addresses concerns regarding safety, ARIA risk, and feasibility of MRI monitoring, and requested that CDEC reconsider the interpretation of lecanemab safety by incorporating new sponsor-provided real-world evidence studies.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- new information provided by the sponsor to address an important clear gap in the evidence identified by CDEC
- feedback from 6 clinical specialists with expertise in the diagnosing and treating patients with AD
- feedback on the draft recommendation from 3 patient groups: the Alzheimer Society of Ontario, Alzheimer Society of Canada, and Toronto Dementia Research Alliance – Lived Experience Advisory Partners Council
- feedback on the draft recommendation from 16 clinician groups: the Canadian Consortium on Neurodegeneration in Aging, Clinique Neuro-Outaouais, Covenant Community Health Centre Lakewood, Memory Clinic at the Douglas Mental Health University Institute, Frédéric Calon, Kelowna Health and Memory Centre, McMaster Geriatrics, Centre hospitalier de l'Université de Montréal, North East Specialized Geriatric Centre, Parkwood Institute (St. Joseph's Health Care), William Osler

Health System, Consortium of Canadian Centres for Clinical Cognitive Research, Toronto Dementia Research Alliance, Toronto Memory Program, Trillium Health Partners, and University of British Columbia Hospital Clinic for Alzheimer Disease and Related Disorders

- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

## CDEC Information

### Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Dr. Dennis Ko, Dr. Christine Leong, Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Carla Velastegui, Dr. Edward Xie, and Dr. Peter Zed

**Initial meeting date:** January 28, 2026

**Regrets:** Four expert committee members did not attend.

**Conflicts of interest:** None

**Reconsideration meeting date:** June 25, 2026

### CDEC Members

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice-Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed

**Regrets:** One expert committee member did not attend.

**Conflicts of interest:** None



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Questions or requests for information about this report can be directed to [Requests@cda-amc.ca](mailto:Requests@cda-amc.ca).