Disease-modifying drugs for Alzheimer disease: implications for people in Canada

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At least 250 000 people in Canada live with mild dementia, and 1.3 million live with mild cognitive impairment.[1–3] Alzheimer disease is implicated in 60%–70% of cases of dementia and 30%–77% of cases of mild cognitive impairment.[4,5] There are no recommended medications for treating people in Canada with mild cognitive impairment, but consensus guidance recommends cholinesterase inhibitors (e.g., donepezil) for symptomatic treatment of dementia caused by Alzheimer disease and memantine for symptomatic treatment of moderate-to-severe dementia caused by Alzheimer disease.[6] No disease-modifying medications for Alzheimer disease have yet been approved in Canada. We discuss disease-modifying medications for Alzheimer disease that have recently been brought to market and approved for use in other jurisdictions, as these may become accessible in Canada in due course.

Key points

- No disease-modifying medications for the treatment of Alzheimer disease have been approved in Canada.
- Lecanemab was the first disease-modifying medication for Alzheimer disease to be granted full approval by the US Food and Drug Administration, and a second such medication — donanemab — is under review by the agency; lecanemab is under review by Health Canada.
- If disease-modifying medications for Alzheimer disease are approved by Health Canada, substantial planning at the health system level is needed to support their implementation, because of high medication costs, and a clear need for post-marketing surveillance, given limited certainty of effect from existing trial data.

In the context of Alzheimer disease, a disease-modifying drug acts to decrease amyloid burden in the brain, thus slowing disease progression. In 2021, aducanumab became the first disease-modifying medication for Alzheimer disease to receive accelerated approval by the US Food and Drug Administration (FDA), which meant that people with Alzheimer disease could access aducanumab sooner, based on trial results showing benefit in a surrogate as opposed to clinical outcome and an unmet treatment need. Aducanumab is a human monoclonal antibody targeting amyloid-β aggregates, including soluble oligomers and insoluble fibrils. According to the amyloid hypothesis, soluble and insoluble amyloid-β peptides trigger a cascade that harms neurons and synapses in the brain, leading to a dementia syndrome.[7] The veracity of the amyloid hypothesis is questioned by some experts because, for example, some people have cerebral amyloid burden without cognitive decline. Nonetheless, the FDA cited a statistically significant improvement in the surrogate outcome of amyloid burden in clinical trials testing aducanumab's efficacy and a large, unmet need for disease-modifying medications for Alzheimer disease in its rationale for granting aducanumab an accelerated approval.[8,9]

The approval of aducanumab by the FDA was controversial, because it set a new precedent for accelerated approval of disease-modifying medications for Alzheimer disease, yet post hoc analyses suggesting aducanumab's efficacy supported this approval.[10] In contrast, Health Canada indicated that the submitted data were insufficient to approve aducanumab, and the application for approval of aducanumab was withdrawn from Health Canada in 2022.[11]

On July 6, 2023, lecanemab became the first disease-modifying medication for Alzheimer disease to be granted full approval by the FDA. Lecanemab is a human monoclonal antibody targeting amyloid-β soluble protofibrils and oligomers with high affinity and has low affinity against amyloid-β monomers and insoluble fibrils.[12–14] The FDA again cited statistically significant changes in the surrogate outcome of amyloid burden in a phase 2 randomized trial and the large, unmet need for disease-modifying medications for Alzheimer disease as rationale for granting lecanemab an accelerated approval.[9,13,15]

Clarity AD, a phase 3 randomized trial, provided evidence for the FDA to convert lecanemab's approval from accelerated to full approval.[16] To be enrolled in Clarity AD, patients were required to be aged 50–90 years and have clinical and biomarker evidence of mild cognitive impairment or mild dementia caused by Alzheimer disease, including positron emission tomography (PET) neuroimaging or cerebrospinal fluid analysis demonstrating amyloid burden, and magnetic resonance neuroimaging could not suggest a likely alternative cause for dementia, such as stroke.[16] Clarity AD found that patients randomly assigned to lecanemab administered intravenously every 2 weeks for 18 months had statistically

significantly lower rates of decline on the Clinical Dementia Rating–Sum of Boxes (CDR-SB), and other measures of cognition and function, but the clinical significance of the study's findings is unclear.[16] The difference in CDR-SB scores between lecanemab and placebo groups was −0.45 points (95% confidence interval [CI] −0.67 to −0.23), but the CDR-SB's minimum clinically important difference (the threshold where someone detects a clinical change) is 1–2 points.[17] Further, the FDA issued a black box warning concerning the risk of amyloid-related imaging abnormalities (ARIA, including edema or effusions, hemorrhages or siderosis). Among patients randomly assigned to lecanemab in Clarity-AD, 193 (21.5%) experienced ARIA, and 31 of these patients (16.1%) developed symptomatic ARIA, including headaches, altered mentation, visual changes, dizziness or seizures.[15,16] Among the patients randomly assigned to placebo, 85 (9.5%) experienced ARIA, and 2 of these patients (2.4%) developed symptomatic ARIA. For this reason, magnetic resonance neuroimaging is recommended to screen for ARIA before the fifth, seventh and fourteenth lecanemab doses, when most ARIA occur.[18] Risk of ARIA was greater in apolipoprotein E (apoE) epsilon 4 homozygotes, so the FDA recommended genetic testing for apoE epsilon 4 before initiating lecanemab.[18] Lecanemab was submitted to Health Canada for review in May 2023.

TRAILBLAZER-ALZ 2, a phase 3 randomized trial, enrolled patients aged 60–85 years with mild cognitive impairment or mild dementia caused by Alzheimer disease who were randomly assigned to donanemab, another disease-modifying medication for Alzheimer disease targeting insoluble cerebral β-amyloid plaques, intravenously administered every 4 weeks for up to 72 weeks.[19] In July 2023, researchers reported that patients in the donanemab group had statistically significantly lower rates of decline on the Integrated Alzheimer Disease Rating Scale (iADRS) and the Mini-Mental State Examination (MMSE), as well as other measures, than the placebo group.[19] However, among patients with low or medium tau burden, the difference in iADRS scores between donanemab and placebo groups was 3.25 points (95% CI 1.88 to 4.62), but the minimum clinically important difference for the iADRS is 5 points in mild cognitive impairment and 9 points in dementia caused by Alzheimer disease. The difference in MMSE scores between donanemab and placebo groups was 0.48 (95% CI 0.09 to 0.87), but the minimum clinically important difference for the MMSE is 1–2 points.[19,20] Donanemab is currently being considered for full approval by the FDA.

Enabling access to disease-modifying medications for Alzheimer disease in Canada would be expensive and challenging for provincial and territorial health care systems. The price for lecanemab is $26 500 per person-year in US dollars.[21] Access to cerebrospinal fluid analysis or PET scan is needed to demonstrate biomarker evidence of Alzheimer disease. Access to PET scans in Canada is limited, and PET neuroimaging for Alzheimer disease would need to become an approved indication.[16,22] Uncertainty about optimal treatment duration and resource use is also a concern because patients randomly assigned to lecanemab in Clarity AD are in an extension phase with follow-up to 69 months and patients enrolled in TRAILBLAZER-ALZ 2 are in an extension phase with follow-up to 198 weeks.[16,19]

The available evidence of effectiveness of these disease-modifying agents for improving the course of Alzheimer disease is limited. Given the risks of ARIA associated with lecanemab, if it is approved by Health Canada and offered, even for limited use, by provincial and territorial drug plans, funding a robust postmarketing adverse effect surveillance program for lecanemab will be essential. Along with consideration of effectiveness, safety and need for substantial resources for implementation, the perspective of people with lived or living experience of dementia will weigh heavily in Canadian policy-makers' deliberations.

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