Technology Guidance

Donanemab and lecanemab

for treating mild cognitive impairment and mild dementia due to Alzheimer's disease

Technology Guidance issued by the Agency for Care Effectiveness based on assessments made by the MOH Drug Advisory Committee and recommendations of the Health Technology Advisory Council

Guidance Recommendations

Donanemab and lecanemab are not recommended for inclusion on the MOH List of Subsidised Drugs for treating mild cognitive impairment and mild dementia due to Alzheimer's disease.

This is because the current available evidence shows that the treatment effects for donanemab and for lecanemab were small with uncertain clinical meaningfulness, and the short trial durations limited the understanding of the treatments' impact over the full course of the disease.

Given the uncertainty in clinical benefit and significant additional healthcare resources required to assess treatment eligibility and risks, as well as for regular magnetic resonance imaging (MRI) monitoring, funding these drugs would not represent a cost-effective use of healthcare resources and could place undue strain on the healthcare system.

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Technology Evaluation

1.1. At the June 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of both donanemab and lecanemab for treating mild cognitive impairment (MCI) and mild dementia due to Alzheimer's disease (AD). This topic was later discussed in September 2025 by the Health Technology Advisory Council ("the Council"), an independent professional body that supports the MOH in determining if financial support for high-cost, high-impact health technologies is appropriate.

1.2. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions and patient experts from local patient and voluntary organisations. Clinical and economic evidence for donanemab and lecanemab was considered in line with their respective registered indications.

1.3. The evidence was used to inform the deliberations based on four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the funding considerations.

Assessments made by the MOH Drug Advisory Committee

Clinical need

2.1. AD is an age-related, progressive neurodegenerative disease and the leading cause of dementia in Singapore. The disease is complex and multifactorial. It is hypothesised that abnormal build-up of amyloid-beta and tau proteins in the brain play key contributory roles in development of the disease.

2.2. The clinical progression of AD can be classified broadly into three stages: preclinical, MCI and dementia due to AD. Amyloid-beta proteins can accumulate for decades during the preclinical stage, without causing symptoms. People with MCI due to AD experience mild but noticeable declines in memory and cognitive abilities that do not disrupt their daily activities. Those with mild dementia due to AD have impairments in memory, cognition, and behaviour that begin to interfere with some aspects of daily life. As the disease progresses, people experience more severe symptoms, and ultimately, the degree of cognitive and functional impairment affects their ability to live independently.

2.3. The current standard drug treatments for AD include acetylcholinesterase inhibitors (donepezil and rivastigmine) and memantine. However, these medications are only approved for treating mild to severe stages of dementia due to AD, and provide symptomatic benefits for some people. The Committee acknowledged there is an unmet need for treatment options that can effectively slow or delay AD progression in its early stages.

2.4. Donanemab and lecanemab are monoclonal antibodies that target and help remove amyloid-beta proteins from the brain. The place in therapy for these drugs would be as an add-on therapy to the current standard of care for people with MCI or mild dementia due to AD, who have confirmed amyloid-beta pathology, to slow disease progression.

2.5. The Committee heard that confirming the presence of amyloid-beta requires either a positron emission tomography scan or cerebrospinal fluid analysis, neither of which is routinely conducted in local clinical practice. Initial genetic testing for *APOE4* would also be required to assess the risk of side effects (brain bleeding and swelling), with subsequent magnetic resonance imaging (MRI) scans needed during treatment to monitor for these complications. The Committee considered that treatment with either donanemab or lecanemab is associated with significant additional healthcare resource use.

2.6. The Committee considered 33 testimonials from local patient experts and carers about the substantial impact of AD on their daily lives. As cognitive and physical abilities progressively declined, people with AD required assistance with daily activities, resulting in loss of independence and social isolation. Carers experienced significant disruption to their work and personal lives due to the demanding and stressful nature of caregiving. Most respondents were receiving current treatments, and expressed mixed views on their effectiveness and side effects. Participation in cognitive, physical and social activities was reported to help maintain functional abilities and improve mental alertness and mood.

2.7. The Committee heard that eight respondents knew about donanemab or lecanemab and expressed concern about potential side effects, including brain bleeding and swelling. Some were reluctant to try these drugs due to concerns about side effects, high cost, lack of a guaranteed cure, or a preference for existing or less invasive treatment options. Overall, respondents considered that new treatments for AD should effectively slow disease progression, help individuals maintain their ability to perform daily activities, preserve quality of life for both people with AD and carers, be affordable, and have manageable side effects.

Clinical effectiveness and safety

3.1. The Committee reviewed clinical evidence from randomised controlled trials (RCTs) for donanemab and lecanemab in patients with MCI or mild dementia due to AD. The main evidence was based on two pivotal phase III placebo-controlled double-blind trials: TRAILBLAZER-ALZ 2 (donanemab) and CLARITY-AD (lecanemab). Three additional RCTs were also reviewed: TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 6 (donanemab) and Study 201 (lecanemab).

3.2. The Committee noted important differences in study population and design between TRAILBLAZER-ALZ 2 and CLARITY-AD. Patients in TRAILBLAZER-ALZ 2 appeared to have more advanced disease than those in CLARITY-AD. In terms of treatment administration, lecanemab was administered regularly throughout CLARITY-AD, whereas patients who received donanemab in TRAILBLAZER-ALZ 2 were switched to placebo (in a double-blind manner) after meeting specified criteria.

3.3. The primary and key secondary outcomes of both trials included changes from baseline for cognitive and functional rating scale scores at approximately 18 months. These rating scales included the integrated Alzheimer Disease Rating Scale (iADRS), and the Clinical Dementia Rating scale – Sum of Boxes (CDR-SB).

3.4. At 18 months, patients treated with donanemab or lecanemab showed smaller declines in iADRS and CDR-SB scores compared to placebo (Table 1). The Committee noted that published minimal clinically important differences (MCIDs) for these outcomes (5 to 9 points for iADRS, and -2.5 to -0.98 points for CDR-SB) represented within-patient changes over time and were not suitable for assessing differences between treatment arms. Overall, the Committee considered that the treatment effects of both drugs were modest and of uncertain clinical meaningfulness.

Table 1: Changes from baseline for iADRS and CDR-SB scores at Week 76 (donanemab vs placebo) and Week 79 (lecanemab vs placebo)

	Donanemab (TRAILBLAZER-ALZ 2)		Lecanemab (CLARITY-AD)	
	LSM or Adjusted mean difference (95% CI), p-value	% difference vs. placebo	LSM or Adjusted mean difference (95% CI), p-value	% difference vs. placebo
iADRS	2.92 (1.51 to 4.33), p<0.001	22.3%	Not studied	
CDR-SB	-0.70 (-0.95 to -0.45), p<0.001	28.9%	-0.45 (-0.67 to -0.23), p=0.00005	27.1%

Abbreviations: CDR–SB, Clinical Dementia Rating scale – Sum of Boxes; CI, confidence interval; iADRS; integrated Alzheimer Disease Rating Scale; LSM, least squares mean.

3.5. The Committee heard that while treatment with either donanemab or lecanemab reduced levels of brain amyloid and plasma phosphorylated tau (p-tau181 and p-tau217) versus placebo, available evidence was insufficient to validate whether these reductions predicted long-term cognitive and functional benefits. The Committee also heard that there were no significant differences in global brain tau deposition between both treatments versus placebo in their respective trials, and considered that overall, the long-term effectiveness of donanemab and lecanemab was highly uncertain.

3.6. In the trials, donanemab and lecanemab treatment arms showed higher rates of amyloid-related imaging abnormalities (ARIA) versus placebo. These abnormalities present as brain swelling (ARIA-E) and/or bleeds (ARIA-H). The risk of ARIA increased with the number of *APOE* ε4 alleles expressed. The Committee noted that while most events were mild to moderate or asymptomatic, ARIA-related deaths were reported with drug treatment.

3.7. The Committee heard that the HSA-approved dosing regimen for donanemab (350 mg, 700 mg, 1050 mg, then 1400 mg every 4 weeks) was informed by results from TRAILBLAZER-ALZ 6, which showed reduced risks of ARIA-E compared to the regimen studied in TRAILBLAZER-ALZ 2 (700 mg for three doses, then 1400 mg every 4 weeks). The Committee noted that while both regimens achieved comparable brain amyloid level reductions (a biomarker outcome) at Weeks 24 and 52, cognitive or functional outcomes were not reported in TRAILBLAZER-ALZ 6, and there was uncertainty whether the HSA-approved regimen would achieve a similar magnitude of clinical efficacy to that observed in TRAILBLAZER-ALZ 2.

3.8. The Committee recognised that significant heterogeneities between the clinical trials limited a robust comparison of the efficacy and safety between donanemab and lecanemab, and considered their relative benefits and risks to be uncertain.

Cost effectiveness

4.1. The Committee reviewed cost-effectiveness analyses conducted by ACE that compared donanemab versus placebo, and lecanemab versus placebo, when used as an add-on to standard of care for people with MCI or mild dementia due to AD. Results from TRAILBLAZER-ALZ 2 and CLARITY-AD were used to inform the economic models for donanemab and lecanemab, respectively.

4.2. Compared to placebo, the base-case incremental cost-effectiveness ratio (ICER) for donanemab was between SG$325,000 and SG$365,000 per quality-adjusted life year (QALY) gained, and more than SG$365,000 per QALY gained for lecanemab. The Committee noted that the ICERs were uncertain due to substantial uncertainties in clinical benefit given the current evidence base.

4.3. When model parameters were varied across the range of possible values, the ICERs remained unacceptably high for both drugs. The Committee noted that the key model drivers included the cost and treatment effectiveness of donanemab and lecanemab, the prevalence of people with amyloid-beta pathology in Singapore, and the quality-of-life measures for people with AD.

4.4. Overall, the Committee considered that donanemab and lecanemab did not represent a cost-effective use of healthcare resources.

Estimated annual technology cost

5.1. The Committee noted that the cost impact to the public healthcare system was estimated to be between SG$1 million and SG$5 million per year for donanemab, and between SG$1 million and SG$5 million in the first year and between SG$5 million and SG$10 million for lecanemab in the fifth year of listing on the MOH List of Subsidised Drugs for the treatment of people with MCI or mild dementia due to AD. The Committee acknowledged that the estimates were highly uncertain and could increase to above SG$10 million per year if more eligible people chose to undergo amyloid-beta testing and receive drug treatment upon subsidy listing.

Summary

6.1. Based on available evidence, the Committee assessed that it was not appropriate to list donanemab and lecanemab on the MOH List of Subsidised Drugs for treating MCI and mild dementia due to AD. This assessment was based on the uncertain extent of clinical benefit and unfavourable cost-effectiveness of both drugs compared with placebo, when given as an add-on to standard of care.

Recommendations of the Health Technology Advisory Council

7.1. At the September 2025 meeting, the Council reviewed the evidence presented in ACE's evaluation of donanemab and lecanemab and considered the assessments made by the MOH Drug Advisory Committee.

7.2. The Council noted that the causes of AD were still not fully understood, and that while donanemab and lecanemab targeted amyloid-beta deposits based on the hypothesis that removing these deposits might slow the disease, other possible causes — such as changes in tau proteins, nerve cell damage, or genetics — were also being studied.

7.3. The Council noted that evidence reviews showed the benefits of donanemab and lecanemab were small compared with placebo, with uncertain clinical meaningfulness for patients and caregivers. The availability of data for approximately 18 months from the randomised phases further limited understanding of the treatments' impact over the full course of the disease.

7.4. The Council noted that both drugs required significant additional healthcare resources, including initial scans and genetic testing to assess treatment eligibility and risks, as well as regular MRI monitoring. Given the uncertain treatment benefits, potential substantial demand for these services, and existing capacity constraints, the Council considered that funding these drugs could place undue strain on the local healthcare system.

7.5. Based on available evidence, the Council concluded that the treatment effects for donanemab and lecanemab had uncertain clinical meaningfulness and did not represent cost-effective use of healthcare resources.

7.6. Therefore, the Council recommended not including donanemab and lecanemab on the MOH List of Subsidised Drugs for the treatment of people with MCI or mild dementia due to AD.

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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