Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1784 Detection of amyloid-beta for inclusion and APOE4 homozygosity for exclusion to inform treatment with donanemab

Applicant: **Eli Lilly Australia Pty Ltd**

Date of MSAC consideration: **31 July 2025**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of the application

The integrated codependent application requested:

- Medicare Benefits Schedule (MBS) funding for (1) apolipoprotein E (*APOE*) genotyping prior to amyloid-beta (Aβ) pathology testing and (2) Aβ pathology testing, in patients with a clinical diagnosis of mild cognitive impairment (MCI) due to Alzheimer Disease (AD) or mild Alzheimer dementia, to determine eligibility for PBS-subsidised treatment with donanemab. Two alternative MBS-funded tests to detect the presence of Aβ pathology: Aβ Positron Emission Tomography (Aβ-PET) of the brain; and Cerebrospinal Fluid (CSF) AD biomarker testing were proposed. In addition, an additional MBS item was also requested for Aβ-PET to assess amyloid clearance in patients receiving treatment with PBS-subsidised donanemab.
- Pharmaceutical Benefits Scheme (PBS) Section 100 (Highly Specialised Drugs Program) Authority Required (Telephone) listing of donanemab for the treatment of patients with early symptomatic AD, defined in the submission as MCI due to AD or mild Alzheimer dementia.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding on the MBS for positron emission tomography (PET) or cerebrospinal fluid (CSF) testing to detect amyloid beta pathology and genetic testing to determine apolipoprotein E genotype in patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) or mild Alzheimer's dementia to assess eligibility for treatment with donanemab. MSAC also did not support public funding of amyloid beta PET testing to monitor response to treatment with donanemab.

MSAC noted that the PBAC considered the potential benefits of donanemab treatment too small and uncertain to justify the high burden of treatment on patients and did not recommend listing donanemab on the PBS at its July 2025 meeting.

MSAC considered that there were several clinical issues with the proposed tests. The application proposed two testing options to detect beta amyloid in the brain: PET scan which was used in the

clinical trial, or CSF testing which was not used in the trial. MSAC considered the two testing options might identify slightly different populations as being eligible for donanemab treatment. MSAC considered these early symptomatic patients, with limited treatment options, might seek both CSF and PET testing over time to access treatment and this was not considered in the application. Additionally, MSAC noted an apparent discordance in the results of the pivotal trial: while a majority (76.4%) of patients treated with donanemab reached amyloid clearance, the delay in clinical progression observed was small (approximately 6 weeks). MSAC noted PBAC considered that there was no evidence that use of donanemab reversed or halted the disease progress. MSAC agreed with PBAC that any possible mechanisms linking reduction in brain beta-amyloid burden and slowing of decline in a person's cognition and functional status remain to be fully elucidated.

MSAC considered the economic model did not appropriately incorporate the tests used to determine eligibility for treatment nor the impact of discordant results from the 2 testing options to detect beta-amyloid pathology. MSAC noted that there would be a substantial net cost to the MBS – estimated to be >$1 billion in the first 6 years of listing for the medical services required to determine eligibility for donanemab and monitor treatment response.

MSAC noted that access to beta amyloid PET scans outside major capital cities is limited because the radiotracer has a short half-life and needs to be administered to the patient shortly after it is manufactured. MSAC noted the capacity constraints in the health system to support diagnosis, treatment and monitoring of patients who use donanemab, including regular monitoring with repeat magnetic resonance imaging scans for amyloid-related imaging abnormalities in the brain. MSAC considered this could contribute to exacerbations in health inequities according to a patient's geographical location or socioeconomic status. MSAC noted that consumers may privately fund donanemab treatment and require the proposed tests to determine eligibility and monitor the effect of donanemab treatment. However, MSAC advised that the proposed tests should not be publicly funded at this time.

Consumer summary
This was a codependent application from Eli Lilly Australia Pty Ltd. It requested Medicare Benefits Schedule (MBS) listings of several tests needed to use donanemab – a medicine that can be used to treat the early stages of Alzheimer disease. The application requested MBS-listing for 2 alternative tests that check if patients have a protein called amyloid-beta in the brain. This protein is linked to Alzheimer disease. The tests are: 1. A brain scan called a PET scan (Aβ-PET) that shows if the protein is there. 2. A test of the fluid around the brain and spine (called cerebrospinal fluid, CSF) to check for signs of Alzheimer disease. Donanemab helps remove clumps of amyloid protein (amyloid plaques) that build up in the brain. People with early Alzheimer disease will need to have one of the two tests to confirm they have amyloid protein. The application also requested MBS-listing of a genetic test for a gene called apolipoprotein E4 (*APOE4*). People with 2 copies of the *APOE4* cannot use donanemab because they are more likely to have swelling or bleeding of the brain with this treatment. This side effect is called amyloid-related imaging abnormalities (ARIA). This swelling or bleeding in the brain can be seen on MRI scans and it does not usually cause any symptoms. Some people with ARIAs can have serious symptoms. Uncommonly, ARIA can be fatal. Apart from the proposed initial tests to determine if patients are eligible to receive publicly subsidised donanemab treatment as mentioned above, the application also requested MBS

Consumer summary
funding for using PET scans of the brain to check for amyloid protein or plaque levels while patients are receiving donanemab. MSAC noted that patients are required to have PET scans of the brain after 6 and 12 months of treatment to check for amyloid protein or plaque levels in the brain. If amyloid plaque is cleared, patients can stop treatment, otherwise will continue treatment up to a maximum of 18 months. Alzheimer disease is one of the main causes of dementia. It is a debilitating condition that affects many Australians. MSAC acknowledged that an effective treatment for Alzheimer disease is needed. MSAC observed that while most patients (76.4%) treated with donanemab achieved amyloid clearance in the main clinical trial, the actual delay in disease progression observed was small—only about six weeks, as measured by the integrated Alzheimer's Disease Rating Scale (iADRS) score, an assessment tool for cognition and daily function in individuals with Alzheimer disease and was used in the main clinical trial. MSAC noted that the PBAC thought the possible benefits of donanemab were too small and uncertain. MSAC considered there were issues with the tests to find beta-amyloid pathology in the brain. The 2 testing options (PET scan or CSF testing) do not always give the same results. In studies where patients had both tests, up to 28% of patients got different results from each test. The clinical trial used PET scans and did not use CSF testing. MSAC considered that it was not known whether people who have a positive CSF test would have the same benefit from donanemab as people who have a PET scan. MSAC considered that patients may not be able to access PET scans outside major capital cities. This is because the scan requires the patient to have an injection with a radiotracer. The radiotracer used for this PET scan is made by a special machine called a cyclotron and needs to be given to the patient very quickly after it is made. This makes it difficult to provide this PET scan outside capital cities. MSAC considered it would also be difficult for patients to access MRI scans in regional areas. CSF testing is an alternative option to a PET scan to see if patients are eligible for donanemab. To have a CSF test, patients need to have lumbar puncture where a needle is inserted into the spine to take out some CSF for testing. MSAC considered this is an unpleasant procedure that has safety issues. MSAC considered the safety of lumbar puncture was not properly considered. MSAC considered that people with symptoms of early Alzheimer disease may have many tests over time to see if they have beta-amyloid. However, this was not properly included in the submission. The *APOE4* gene is inherited. People with one or two copies of the gene are more likely to have Alzheimer Disease. MSAC considered the results of *APOE4* testing may affect family members of the person tested. This was also not considered in the submission. MSAC considered it could not assess value-for-money because the economic model did not properly include the tests. MSAC noted that apart from the initial tests required prior to donanemab treatment, there are also monitoring tests required for patients receiving donanemab. Patients are required to have regular magnetic resonance imaging (MRI) scans of the brain to make sure that there are no serious side effects in the brain. A brain MRI is recommended before the second, third, fourth and seventh dose (usually 6 months) of treatment. MSAC noted that the cost of testing was expected to cost approximately >$1 billion over 6 years and that this did not include the cost of the medicine.

Consumer summary
MSAC considered there is a high burden of the diagnosis, testing and monitoring. Patients would need multiple tests and scans before and after treatment is started. These tests would likely result in out-of-pocket costs for patients, with an even greater burden for rural and regional patients who might have to travel to metropolitan centres for the tests and/or treatment. MSAC noted that the specialised clinics that would be needed to treat such patients are currently facing capacity issues, and they might not have the capacity for additional patients. MSAC did not support funding for the tests used to decide if patients should have donanemab and monitor treatment. This is because the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend listing donanemab on the PBS. The PBAC considered the potential benefits of the drug to be too small and uncertain and this, combined with the treatment burden on both patients and the health system, makes it unsuitable for listing on the PBS. MSAC considered that there were too many issues with the proposed tests, making it difficult to determine the safety, clinical effectiveness and value for money with the proposed services for listing on the MBS. **MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing** MSAC did not support public funding of *APOE* genotyping and amyloid pathology testing to determine eligibility to access donanemab. This was because the PBAC considered the potential benefits too small and uncertain to justify the burden of this treatment on both patients and the health system. MSAC considered that there were many issues with the proposed tests, making it difficult to determine the safety, clinical effectiveness and value for money with the proposed services for listing on the MBS. The potential financial impact to the MBS would also be substantial. In addition, there are multiple implementation, equity and access issues that would need to be resolved.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this codependent application from Eli Lilly Australia Pty Ltd was for the proposed MBS listing of Aβ pathology testing using either Aβ-PET scanning of the brain or CSF AD protein biomarker testing (amyloid and tau proteins), and *APOE* genotyping before Aβ pathology testing, in patients with a clinical diagnosis of MCI due to AD or mild Alzheimer dementia (hereafter referred to collectively as early symptomatic AD), to determine eligibility for PBS-subsidised donanemab treatment.

MSAC noted that donanemab is the first drug to be registered on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)-for the treatment of patients with early symptomatic AD and who are *APOE4* heterozygotes or non-carriers.

MSAC noted that there were 2 relevant previous applications (MSAC application 1643 and 1738) which requested public funding for Aβ-PET scan of the brain and CSF AD protein biomarker testing, to determine eligibility for a PBS-subsidised drug (aducanumab and lecanemab, respectively) in patients with early-stage AD. However, neither was TGA-registered nor progressed to MSAC for consideration.

MSAC noted that the current application bypassed PASC due to the existence of a relevant PICO Confirmation ratified by PASC in April 2021 (MSAC application 1643). However, MSAC noted that *APOE* genotyping was not included as part of the proposed clinical management algorithm in the Ratified PICO Confirmation.

MSAC acknowledged that there is a high clinical need for effective treatments for early symptomatic AD. MSAC noted that dementia was the second leading cause of burden of disease in Australia in 2023, behind coronary heart disease, and was the second leading cause of death in 2022.[1]

MSAC noted the summary of public consultation input and welcomed the consumer (n=3) and organisation (n=5) feedback received. MSAC noted that the organisation feedback was broadly supportive while the individual feedback was mixed.

The applicant was granted a hearing at the MSAC meeting in July 2025.

MSAC noted that PBAC considered the potential benefits of donanemab treatment too small and uncertain to justify the high burden of treatment on patients and the health system and did not recommend the proposed listing of donanemab on the PBS at its July 2025 meeting.

MSAC noted that the TGA did not approve the use of donanemab in *APOE4* homozygous patients owing to the higher rates of amyloid-related imaging abnormalities (ARIA) observed in these patients receiving donanemab treatment in clinical trials. MSAC noted that the current application proposed patients to undergo blood-based polymerase chain reaction (PCR) genotyping to determine their *APOE4* status. Patients who were found to be *APOE4* homozygous would not be eligible for donanemab treatment. While patients identified as *APOE4* non-carriers or heterozygotes would be offered Aβ pathology testing.

MSAC noted that while the pivotal TRAILBLAZER-ALZ 2 trial (TB2) required participants to have amyloid pathology (≥37 Centiloids) assessed with ^{18}F-florbetapir[13] or ^{18}F-florbetaben[14] PET and presence of tau pathology assessed by ^{18}F-flortaucipir PET imaging to be eligible, the submission did not propose using testing for tau pathology. MSAC considered that further clarification on the role of tau testing to determine eligibility to donanemab treatment would be required. MSAC also considered that advice from the Australasian Association of Nuclear Medicine Specialists (AANMS) regarding the availability of tau testing in Australia would be required.

MSAC considered the broader systems requirements associated with diagnosis and the administration of the donanemab infusion were not adequately addressed in the submission. MSAC noted a specialist multidisciplinary setting is required for diagnosis and treatment, and noted the department's advice that attendance items could currently be used to support administration, but these items do not enable nurse-led delivery. MSAC considered the model of care, including the administration of the infusion, required review to determine whether additional MBS items are required. MSAC noted the department's advice that the requirement for each patient undergoing donanemab treatment to have regular MRI scans to assess for ARIA would place significant pressure on patient access to MRI scans more broadly. MSAC noted that the prevalence of *APOE4* heterozygous and homozygous patients in the Australian population was unclear, with estimates of 15–30% *APOE4* heterozygosity and 2–4% homozygosity in the whole Australian population. MSAC considered that both proportions would likely be higher in the early symptomatic AD population (as the *APOE4* allele is associated with an increased risk of developing the disease) and that this uncertainty would flow on to the financial impact.

MSAC reviewed the safety and effectiveness of the proposed *APOE4* genotyping. MSAC noted that *APOE4* genetic testing would be straightforward and that many laboratories in Australia could perform the test. MSAC considered the proposed MBS fee ($154.00) for *APOE4* genotyping

[1] *Dementia in Australia*, Australian Institute of Health and Welfare, web report, last updated 13 September 2024 [available: https://www.aihw.gov.au/reports/dementia/dementia-in-aus/contents/summary?s].

to be appropriate, accounting for a relatively small proportion of the overall costs of diagnostics, monitoring and treatment. MSAC had no concerns regarding the performance of the test. MSAC considered the results of *APOE4* genetic testing may have implications for family members because having one or two copies is an inherited risk factor of developing Alzheimer disease. This was not addressed in the submission.

MSAC noted that most of the clinical effectiveness and safety data for amyloid testing and subsequent donanemab treatment were derived from the TB2 trial.

MSAC reviewed the evidence for safety and effectiveness of amyloid testing. MSAC noted that the positive predictive value (PPV) of Aβ-PET for Alzheimer disease dementia was affected by age and clinical confidence in pre-test Alzheimer diagnosis, with a PPV of 0.17-0.98, and was also affected by *APOE4* status.[2] In addition, MSAC noted from the commentary that the discordance between the PET and CSF test results for Aβ testing could be as high as 28%. MSAC also noted that the CSF test is less sensitive and less specific than Aβ-PET. MSAC considered that the impact of discordant results (e.g. positive CSF result but negative Aβ-PET for a patient) on costs and clinical outcomes were unknown. Therefore, MSAC considered that the submission did not present any evidence to support the safety and effectiveness of CSF testing in detecting amyloid pathology to access donanemab. Given the limited availability and geographical inequity of access to PET machines that perform Aβ-PET scans in Australia, MSAC considered that CSF testing would likely be of particular significance in the Australian context, and this was not adequately addressed in the submission.

MSAC considered that as CSF tests must be performed via lumbar puncture, patients are exposed to potential safety and experiential issues from the procedure, which are not present for patients undergoing Aβ-PET scans.

MSAC also considered that some patients might try to access both PET and CSF testing options to access donanemab. MSAC considered that patients with early symptomatic AD have limited treatment options and so might seek multiple tests including both CSF and PET imaging over time to access donanemab treatment, an issue not considered in the submission.

MSAC agreed with the department's advice that the MBS fee for the proposed PET scan, if approved, should be reduced from the applicant's proposed fee of $2,200 to $1,800. MSAC noted that the reduced fee was informed by consultation input and other MBS PET items, including those which use specialised radiotracers.

MSAC agreed with the submission's claim that amyloid testing (using Aβ-PET or CSF testing), followed by treatment with donanemab and standard of care (SOC), has an inferior safety profile compared to no testing and treatment with SOC.

MSAC noted that the PBAC considered that donanemab had a very modest impact on the measures of cognition and function. The clinical trial showed donanemab can potentially slow the progression of early AD by approximately 6 weeks. The PBAC considered that it was highly uncertain if the degree of slowing in clinical progression was clinically meaningful or if it would produce a noticeable benefit to patients and caregivers.

MSAC noted that a majority (76.4%) of donanemab-treated patients reached amyloid clearance, as measured by amyloid PET, after 76 weeks of treatment compared to few (0.3%) placebo patients. However, the 6-week delay in clinical progression was small. MSAC noted that the

[2] Bergeron D, Ossenkoppele R, Jr Laforce R. Evidence-based Interpretation of Amyloid-β PET Results: A Clinician's Tool. *Alzheimer Dis Assoc Disord*. 2018 Jan-Mar;32(1):28-34. doi: 10.1097/WAD.0000000000000239. PMID: 29334498.

association between decreasing amyloid pathology and delay in cognitive decline was reiterated by the applicant in the pre-MSAC response and at the hearing. However, MSAC noted that PBAC considered that donanemab had a very modest impact on the measures of cognition and function. MSAC agreed with PBAC that any possible mechanisms linking reduction in brain beta-amyloid burden and slowing of decline in a person's cognition and functional status remain to be fully elucidated.

MSAC noted that the submission presented a modelled economic evaluation (cost-utility analysis) comparing donanemab treatment versus SOC and that the base case incremental cost of donanemab treatment was $35,000 to <$45,000 per quality-adjusted life year (QALY) gained, when compared to SOC. MSAC noted the PBAC considered that the economic model was overly optimistic and the listing would not be cost-effective at the requested price.

MSAC noted that patients entered the economic model at the point of treatment and that the commentary considered this reasonable as testing costs for all patients considered for the medicine were included in the model. MSAC agreed with the joint MSAC/PBAC ESCs that patients should have entered the model at the point of testing, incorporating consideration the impact of false positives/false negatives. MSAC considered that the economic evaluation should consider the whole population, both tested and treated populations, especially in the context of two proposed alternative tests for Aβ pathology which might have discordant results to determine access to a drug and the pivotal TB2 trial used only one of the tests. MSAC considered that the economic model should incorporate the downstream impact of false positive (e.g., potential harms from unnecessary donanemab treatment and associated monitoring) and false negative test results (e.g., not eligible to donanemab treatment).

MSAC considered the submission's model assumption that 40% of patients would be treated to clear, as assessed by PET scanning, to be uncertain. MSAC considered that the proportion of patients treated to clear or treated to the maximum of 18 months as per the TGA approved product information for donanemab, would be influenced by the availability of PET scanning facilities.

MSAC considered the cost-effectiveness result presented to be highly uncertain due to multiple issues with the modelling assumptions and input parameters some of which were arbitrary and not well justified.

- MSAC considered that it was inappropriate that patients entered the economic model at the point of treatment rather than at the point of testing.
- MSAC noted the potential issue regarding test discordance between testing for Aβ pathology using brain PET scan and CSF and that the discordance could range from 2 to 28%. MSAC noted that the tests discordance might result in slightly different patient populations be identified as eligible to access donanemab, an issue the submission did not consider.
- MSAC considered the submission's assumption of a 50/50 split of patients undergoing Aβ-PET brain scan or CSF AD biomarker testing to be inadequately supported and uncertain. The submission did not consider some patients might seek repeat testing over time either.
- MSAC noted that the submission's economic result was sensitive to the proportion of patients treated to clear or treated to 18 months: assuming 100% of patients treated to 18 months (base case 60%), the incremental cost-effectiveness ratio (ICER) increased (REDACTED %) from $35,000 to <$45,000 to $45,000 to <$55,000/QALY gained.

MSAC considered a more appropriate approach to the economic evaluation would be to include the total target patient population (tested and treated) including those who would undergo the proposed testing (*APOE4* and amyloid testing); incorporate consideration of discordant results

from Aβ-PET and CSF AD biomarker testing, including any relevant downstream costs and consequences.

MSAC noted the evaluation's revised financial estimates pre-ESC on the net cost to the MBS was $100 million to <$200 million in Year 1 and rising to $300 to <$400 million in Year 6 of listing (totalling >$1 billion in Years 1-6). MSAC considered the financial cost for the medical services required to determine eligibility for donanemab and monitoring of treatment response and adverse events to be substantial. MSAC considered the submission's approach to estimate the eligible tested and treated patient numbers from based on system capacity to be inappropriate and advised that the patient numbers should be estimated based on eligibility for the clinical services instead. MSAC considered the financial estimates uncertain due to uncertainty in the prevalence of *APOE4* homozygosity in Australia and the uptake rates for Aβ-PET brains and CSF AD biomarker testing.

MSAC noted the various potential health system capacity issues, e.g., access to radiotracers, PET scans and brain MRIs required for diagnosis and monitoring purposes, especially for patients residing in regional and rural areas. Capacity issues also exist for the specialised multidisciplinary clinics that are essential for providing diagnosis and treatment. MSAC noted the applicant stated during the hearing that the capacity for additional CSF testing was high. However, MSAC considered that there would likely be access issues to PET and MRI especially for regional and rural patients for diagnosis and monitoring. MSAC also considered the capacity of Australian health system to provide equity of safe access to treatment uncertain, given the frequent clinical monitoring and brain MRI scans required especially during the early stages of treatment, and with considerable opportunity costs for other patient populations who required access to these services.

After considering the strength of the evidence the submission presented in relation to comparative safety, clinical effectiveness, cost-effectiveness and the financial impact of the proposed testings (+ donanemab treatment) versus no testing (+ SOC), MSAC did not support public funding of *APOE* genotyping nor Aβ pathology testing (Aβ-PET, CSF AD biomarker testing) for patients with early symptomatic AD to determine eligibility for donanemab treatment. MSAC did not support public funding of Aβ-PET to assess amyloid clearance in patients on donanemab treatment either.

MSAC noted that PBAC considered the potential benefits of donanemab treatment too small and uncertain to justify the high burden of treatment on patients and did not recommend listing donanemab on the PBS at its July 2025 meeting.

MSAC considered that there were several clinical issues with the proposed tests. The application proposed two testing options to detect beta amyloid in the brain: PET scan which was used in the clinical trial, or CSF testing which was not used in the trial. MSAC considered the two testing options might identify slightly different populations as being eligible for donanemab treatment. Additionally, MSAC considered these early symptomatic patients are a vulnerable group seeking any potential treatment for their condition, and they might seek multiple tests including both CSF and PET over time to access treatment and this was not considered in the submission.

MSAC considered the economic model did not appropriately incorporate the tests used to determine eligibility for treatment nor the impact of discordant results from the 2 testing options to detect beta-amyloid pathology. MSAC noted that there would be a substantial net cost to the MBS – estimated to be >$1 billion in the first 6 years of listing for the medical services required to determine eligibility for donanemab and monitor treatment response.

MSAC noted that access to Aβ-PET scans outside major capital cities is limited because the radiotracer has a short half-life and needs to be administered to the patient shortly after it is

manufactured. MSAC noted the lack of current health system capacity to support diagnosis, treatment and monitoring of patients who use donanemab, including regular monitoring for amyloid-related imaging abnormalities in the brain. MSAC considered this could contribute to exacerbations in health inequities according to a patient's geographical location or socioeconomic status. Therefore, MSAC advised that the proposed tests should not be publicly funded at this time.

MSAC acknowledged that a full resolution of the system capacity and implementation issues are matters for the health system and are beyond the applicant's ability to resolve.

MSAC advised that future co-dependent applications for anti-amyloid treatments should be considered by PASC, ESC and MSAC. MSAC advised that future co-dependent applications for anti-amyloid treatments should consider the need for any other testing regimens such as tau testing, emerging blood-based biomarker testing, alternative methods (e.g., biochemical) for *APOE4* carrier status testing, etc.

4. Background

This was the first time MSAC considered *APOE* genotyping and testing for Aβ pathology via Aβ-PET and CSF AD biomarker testing.

There were two relevant MSAC applications which requested public subsidy for Aβ-PET and CSF AD biomarker testing in patients with early-stage AD to determine access to a PBS-listed treatment. Neither application progressed to consideration by MSAC.

Application 1643 requested the testing options to determine access to aducanumab. PASC considered the application in December 2020 and April 2021, with the subsequent ratification of a PICO Confirmation. However, the application[3] did not progress to evaluation by PBAC and MSAC.

Application 1738 requested the testing options to determine access to lecanemab. The application bypassed PASC and was scheduled to be considered by MSAC/PBAC ESCs in June 2024. However, the application was withdrawn and did not progress further. The TGA delegate decided not to register lecanemab on the basis that the demonstrated efficacy did not outweigh the safety risks associated with the use of this medicine in October 2024 and confirmed its decision not to register in March 2025.[4]

[3] The sponsor announced its business decision to discontinue the development and commercialisation of ADUHELM® (aducanumab-avwa) 100 mg/mL injection, terminate the ENVISION clinical study and to reprioritise its resources in AD. The sponsor stated that the decision was not related to any safety or efficacy concerns (source: https://investors.biogen.com/news-releases/news-release-details/biogen-realign-resources-alzheimers-disease-franchise).

[4] The TGA Delegate considered the provided clinical study data demonstrated that patients treated with lecanemab showed some slowing in disease progression in some populations compared to those given a placebo, but this was not demonstrated in all populations covered by the therapeutic indications proposed by the sponsor. "The Delegate found that both safety and efficacy are satisfactorily established for *APOE4* noncarriers. In the course of the reconsideration of the initial decision, the Delegate proposed an alternative indication limited to *APOE4* noncarriers, however, the Applicant indicated it is not willing to agree to seek an indication restricted to this population. The Applicant proposed that *APOE4*-heterozygotes should be treated in specialist centres and supervised by physicians with expertise in monitoring for ARIA. However after consideration, the Delegate was not satisfied that this wording would be specific enough to support clinicians and address the outstanding safety concerns for patients who are *APOE4* heterozygous carriers" (source: https://www.tga.gov.au/news/news/tga-confirms-decision-not-register-lecanemab-leqembi).

5. Prerequisites to implementation of any funding advice

Test

The application did not provide information about the regulatory status of *APOE* genotyping in Australia. There were several commercially available *APOE* PCR-based genotyping tests, such as TaqMan™ Genotyping Assays (Applied Biosystems) and the Human *APOE* genotypes (ε2/ε3/ε4) Real Time PCR Kit (Creative Biogene). However, their status with the TGA was unknown. It was also possible that laboratories currently offering this test in Australia might be using an in-house IVD.

According to the Royal College of Pathologists of Australasia (RCPA) website,[5] *APOE* genotyping to identify the ε4 (*APOE4*) variant was available through four member laboratories in Australia; Genomic Diagnostics (VIC) Pathology Queensland (QLD), Queensland Medical Laboratory Pathology (QLD). and the Royal Prince Alfred Hospital, Dept. Medical Genomics (NSW). Timely processing of all patient samples would require increased capacity to meet demand, which would likely require additional laboratories being accredited to offer *APOE* genotyping. A Quality Assurance Program (QAP) would also need to be established.

Information about these tests could only be sourced from the Royal Prince Alfred Hospital, which used the Taqman RT-PCR genotyping assay by Thermo Fisher. Thermo Fisher Scientific Australia Pty Ltd was registered on the ARTG for Human genetics-related IVDs (ARTG entry 461285).

The application reported that there were no TGA-approved radiopharmaceuticals for Aβ-PET. However, as radiopharmaceuticals were made to order, they could be considered exempt from TGA registration under the 'extemporaneous compounding' exemption. Currently in Australia, Cyclotek was the only commercial company manufacturing Aβ-PET radiopharmaceuticals in Australia. According to the submission and the consultation input received, Cyclotek, has manufacturing sites (cyclotrons) in Victoria (n=2), New South Wales (n=1) and Queensland (n=1), with 2 additional sites (one in Brisbane, QLD and the other in NSW) expected to be operational in 2026. A second commercial company, Cyclowest's new cyclotron radiopharmaceutical production facility in Perth, Western Australia, might also be able to supply Aβ-PET radiopharmaceuticals in the future. Other producers of Aβ-PET radiopharmaceuticals in Australia included hospital nuclear medicine departments with onsite cyclotrons.

However, given the short half-life of these radiotracers (~110 minutes), they would need to be used by PET scanning facilities located nearby, limiting the number of facilities with PET machines that could offer this service in Australia. Cyclotek informed in its consultation input that it employed a de-centralised manufacturing and distribution model to establish reliable and consistent supply of radiopharmaceutical products nationally, across both metropolitan and regional Australia. Cyclotek informed that its radiopharmaceutical products were manufactured across the east coast of Australia and then distributed to hospitals and/or clinical imaging sites nationally via its extensive logistics network, using a combination of road and air freight.

The applicant confirmed that in Australia, the commercially available Elecsys® AD CSF portfolio has been included on the ARTG 200275 as class 2 IVDs, and includes the following assays:

- Elecsys® β-Amyloid (1-42) CSF
- Elecsys® Phospho-Tau (181P) CSF

[5] https://www.rcpa.edu.au/Manuals/RGTL/Genes/Gene-Details?Symbol=APOE

- Elecsys® Total-Tau CSF

Two pathology testing laboratories received National Association of Testing Authorities (NATA) accreditation for the use of the Elecsys® CSF assays; the National Dementia Diagnostics Laboratory (NDDL), located at The Florey in Melbourne, Victoria and Concord Hospital, Sydney, NSW. Timely processing of patient samples would require increased capacity to meet demand at these two pathology laboratories as well as additional laboratories being accredited to offer the service. This would also require the establishment of a QAP to ensure the reliability and reproducibility of results between diagnostic laboratories.

Drug

Donanemab was TGA-registered (21 May 2025) for the treatment of patients with MCI due to AD and Mild Alzheimer dementia who are APOE4 heterozygotes or non-carriers.

The TGA-approved Product Information stated that "Beta amyloid evidence consistent with AD should be confirmed using a validated test prior to initiating treatment." It also recommended that:

- Treatment should be maintained until amyloid plaques are cleared, as confirmed using a validated method, up to a maximum of 18 months.
- Treatment should be continued for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible.

6. Proposal for public funding

Test

The application requested 4 new MBS item numbers.

APOE *genotyping*

The application requested MBS funding for *APOE* genotyping to determine eligibility for PBS-subsidised donanemab treatment. The TGA-approved PI states that donanemab is indicated in patients who are *APOE4* heterozygotes or non-carriers but not patients who are *APOE4* homozygotes with the greatest risk of amyloid-related imaging abnormality (ARIA). Table 1 presented the applicant's proposed MBS item descriptor for *APOE* genotyping to determine eligibility for PBS-subsidised donanemab treatment, with the department's proposed edits in *red italics*.

Table 1 Requested MBS item for *APOE* genetic testing in the application and the department's proposed edits

Category 6 – Pathology Services P7 - Genetics
Item ~~descriptor~~ XXXX ~~Apolipoprotein E genotyping~~ Genetic testing to determine apolipoprotein E ε4 (APOE ε4) genotype as requested by a specialist or consultant physician for patients with Mild Cognitive Impairment (MCI) due to Alzheimer disease ~~and~~*or* Mild Alzheimer dementia ~~who are being considered for therapy with donanemab~~ *to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Schedule*. *Applicable once per lifetime.* Fee: $154.00 Benefit: 75% = $115.50 85% = $130.90 ~~Explanatory note:~~ ~~Prior to ordering this test, the ordering practitioner should ensure that the patient meets other eligibility criteria for PBS-subsidised treatment with donanemab including having a (standardised) Mini-Mental State Examination Score of 20 or more, and that the patient is eligible for treatment based on magnetic imaging results from a scan performed within the previous 6 months~~

Source: Table1.14, page 50 of the submission.
Department's proposed edits in ~~strikethrough texts~~ and *red italics.*
Note: The application proposed a fee of $154 for *APOE ε4* genotyping, based on Sonic Genetics 2023.

Aβ diagnostic imaging and pathology testing

The application requested MBS funding for two testing modalities, Aβ-PET and CSF AD biomarker testing, either of which could be used, to assess the presence of Aβ pathology in patients with early symptomatic AD to determine eligibility for PBS-subsidised donanemab treatment. Table 2 presented the application's requested MBS item for Aβ-PET and the department's proposed edits.

Table 2 Requested MBS item for Aβ-PET in the application and the department's proposed edits

Category 5 – Diagnostic Imaging Services *Group I4 – Nuclear Medicine Imaging* *Subgroup 2 - PET*
Item ~~descriptor~~ YYYY Beta-amyloid positron emission tomography (PET) study of the brain, requested by a specialist or consultant physician, for the evaluation of patients with a clinical diagnosis of mild cognitive impairment due to Alzheimer disease or mild Alzheimer ~~disease~~*dementia*, to determine eligibility for treatment with ~~donanemab~~*an anti-amyloid monoclonal antibody agent to treat Alzheimer disease* under the Pharmaceutical Benefits Scheme (PBS), if: • the patient considered for this service also meets specific PBS eligibility criteria ~~for treatment with donanemab other than the criterion relating to amyloid status~~; and • the patient has not previously been treated and is not currently undergoing treatment with ~~donanemab~~*the pharmaceutical.* Fee: ~~$2,200~~**$1,800.00* Benefit: 75% = ~~$1,650~~*$1,350.00* 85% = ~~$1870~~*$1,697.60***

Source: Table 1.15, page 51 of the submission
Department's proposed edits in ~~strikethrough texts~~ and *red italics.*
* According to the submission, the proposed fee has been informed by researchers currently utilising Aβ radiopharmaceuticals.
** The 85% benefit reflects the 1 November 2024 Greatest Permissible Gap (GPG) of $102.40.

Aβ-PET examinations should be performed by, or under the supervision of, a physician specialised in nuclear medicine and certified by accrediting boards, or a registered or certified nuclear medicine technologist. Aβ-PET results should be interpreted by specialists who have completed the appropriate training programs provided by the manufacturers of the radiotracers.

The department informed that MBS item 61505 for CT attenuation scan (MBS fee $100.00) would be co-claimed with this item.

Table 3 presented the application's requested MBS item for CSF AD biomarker testing and the department's proposed edits.

Table 3 Requested MBS item for CSF AD biomarker testing in the application and the department's proposed edits

Category 6 – Pathology Services *P2 – Chemical (TBC)*
Item ZZZZ Analysis of amyloid and tau proteins in cerebrospinal fluid, requested by a specialist or consultant physician, from a patient with a clinical diagnosis of mild cognitive impairment due to Alzheimer disease or mild Alzheimer disease, to determine eligibility for *a relevant* treatment ~~with donanemab~~ under the Pharmaceutical Benefits Scheme (PBS), ~~if:~~ • ~~the patient considered for this service also meets specific PBS eligibility criteria for treatment with donanemab other than the criterion relating to amyloid status; and~~ • ~~the patient has not previously been treated and is not currently undergoing treatment with donanemab~~. Fee: $400 Benefit: 75% = $300 85% = $340

Source: Table 1.16, page 51 of the submission
Department's proposed edits in ~~strikethrough texts~~ and *red italics.*
Note: The application proposed an MBS item fee of $400 for CSF AD biomarker testing, based on the current cost of testing at the NDDL.

CSF collection, via lumbar puncture, is usually performed by a medical officer with relevant training, which may include neurologists, anaesthetists, and interventional radiologists. In some circumstances, a general practitioner or nurse practitioner may also perform a lumbar puncture. CSF AD protein biomarker testing must be performed at a NATA-accredited laboratory for reimbursement on the MBS.

The costs associated with the lumbar puncture including performing the lumbar puncture would be reimbursed under MBS item 39000 for an MBS fee of $85.75 and the commentary noted that the use of CT to guide the procedure would be reimbursed under MBS item 57341 for a fee of $516.45.

Costs for additional procedures required for the lumbar puncture included: anaesthetic (MBS item 21945 – $112.75), anaesthetic consultation (MBS item 17610 – $49.75), time modifier, depending on anticipated duration of procedure (MBS item 23010 – $22.55 or 23025 – $45.10), and age or comorbidity modifiers (MBS items starting at 25000 – $22.55).

Table 4 presented the application's requested additional MBS item for Aβ-PET to assess amyloid clearance in patients receiving treatment with PBS-subsidised donanemab. These scans were expected to occur in weeks 24 and 52.

Table 4 Requested MBS item for Aβ-PET monitoring to assess amyloid clearance in the application and the department's proposed edits

Category 5 – Diagnostic Imaging Services *Group I4 – Nuclear Medicine Imaging* *Subgroup 2 - PET*
Item ~~descriptor~~ AAAA Beta-amyloid positron emission tomography (PET) study of the brain for the evaluation of patients currently receiving treatment with ~~donanemab~~*an anti-amyloid monoclonal antibody agent intended to treat Alzheimer disease* under the Pharmaceutical Benefits Scheme (PBS) if: • the service includes a quantitative comparison of the results of the study with the results of a beta-amyloid study of a normal brain from a reference database. Applicable up to a total of two services. Fee: ~~$2,200~~**$1,800.00* Benefit: 75% = ~~$1,650~~*$1,350.00* 85% = ~~$1870~~*$1,697.60***

Source: Table 1.17, page 51 of the submission. Department's edits in ~~strikethrough~~ texts and red *italics*.
* According to the submission, the proposed fee has been informed by researchers currently utilising Aβ radiopharmaceuticals.
**The 85% benefit reflects the 1 November 2024 Greatest Permissible Gap (GPG) of $102.40.

The department informed that MBS item 61505 for CT attenuation scan (MBS fee $100.00) would be co-claimed with this item.

MRI monitoring to detect ARIAs

The increased frequency of ARIA events occurring in patients receiving donanemab (mostly within the first 24 weeks of treatment) requires careful monitoring, both by MRI and by monitoring for the emergence of symptoms. The TGA-approved PI for donanemab stated that a recent (within 6 months) baseline brain MRI should be available prior to initiating treatment. An MRI should be performed prior to the 2nd dose (one month), prior to the 3rd dose (two months), prior to the 4th dose (usually 3 months) and prior to the 7th dose (usually six months). An MRI may also be indicated if symptoms that may be indicative of an ARIA occur, such as headache, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures. The PI also recommends consideration of a follow-up MRI to assess for resolution of ARIA oedema/effusions or stabilisation of ARIA haemorrhage/hemosiderin deposition 2-4 months after initial identification.

This application proposed to use MBS Item 63004 (MRI—scan of head) to inform the cost of MRI monitoring. The sponsor sought feedback from the Department whether a standalone MBS item would be required for MRI monitoring of patients treated with donanemab. The department proposed that MRI items specific to baseline scanning (Table 5) and asymptomatic ARIA monitoring during treatment (Table 6) are required.

Table 5 Department-proposed MBS item for a baseline MRI scan prior to treatment

Category 5 – Diagnostic Imaging Services 15. Magnetic Resonance Imaging Subgroup 1 – Scan of head – for specified conditions
Item XXXX Magnetic resonance imaging (MRI) scan of the head (including MRA, if performed) for the baseline assessment of patients who will be treated with an anti-amyloid monoclonal antibody agent intended to treat Alzheimer disease under the Pharmaceutical Benefits Scheme (PBS), to ensure the patient does not have pathology which would preclude treatment with this agent. One scan per patient. Fee: $452.05* Benefit: 75% = $339.04 85% = $384.24

*Proposed fee based on MBS Item 63004, updated to the current schedule fee as of 1 July 2025.

Table 6 Department-proposed MBS item for monitoring MRI scan during treatment

Category 5 – Diagnostic Imaging Services 15. Magnetic Resonance Imaging Subgroup 1 – Scan of head – for specified conditions
Item XXXX Magnetic resonance imaging (MRI) scan of the head (including MRA, if performed) for the evaluation of patients currently receiving treatment with an anti-amyloid monoclonal antibody agent intended to treat Alzheimer disease under the Pharmaceutical Benefits Scheme (PBS) to ensure the patient does not have pathology which would preclude further treatment with this agent. The assessment will be performed to determine the continuing safety of treatment. Applicable not more than four times in a 12-month period Fee: $452.05* Benefit: 75% = $339.04 85% = $384.24

*Proposed fee based on MBS Item 63004, updated to the current schedule fee as of 1 July 2025.

Drug

This integrated codependent application requested PBS Section 100 (Highly Specialised Drugs Program) Authority Required (Telephone) listing of donanemab for the treatment of patients with early symptomatic AD, defined as MCI due to AD or Mild AD.

The clinical eligibility criteria requires that the patient must have a baseline Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE) score of 20 or more, and that i) the condition must have the presence of beta-amyloid positivity in the brain or CSF, ii) the patient must not be contraindicated to treatment with this drug on the basis of MRI brain findings, and iii) the patient must be an *APOE4* heterozygote or non-carrier. The patient must be treated by a neurologist, geriatrician, or psychiatrist.

7. Population

Test

AD is a progressive neurodegenerative brain disease affecting cognition (memory, language, executive function e.g., problem-solving), and visuospatial function. Changes in behaviour (mood and personality), along with decreased or poor judgment and sleep disturbances, also occur. As the disease progresses, patients lose the ability to perform activities of daily living, such as paying bills, bathing and dressing. The submission reported that, in Australia, the number of people with AD, including both MCI and Alzheimer dementia, is expected to double from approximately 600,000 in 2024 to 1,200,000 by 2050 as a result of an ageing and growing population.

AD is characterised by the presence of extracellular neuritic plaques in the brain containing Aβ peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. Other changes in the brain include neuroinflammation, gliosis, neuronal loss, and synaptic changes.

The commentary considered that whilst there is a strong link between the presence of Aβ plaques and the development of AD, it is not absolute. Not all individuals with Aβ plaques will develop AD. Additionally, Aβ plaques are present for many years prior to symptom development, suggesting that long-term damage to the brain may have already occurred. The prognosis of disease after removal of Aβ plaques from the brain has yet to be established.

The *APOE4* allele is the most significant genetic risk factor for late-onset AD and is associated with an increased risk of developing the disease. Up to 25% of the population and approximately 60-75% of AD patients in clinical studies are *APOE4* carriers. Heterozygous carriers of *APOE4* have a 3–4-fold increased risk of developing late-onset AD, while homozygous carriers have a 9–15-fold higher risk compared with having the *APOE ε3* (*APOE3*) allele.

APOE4 has been shown to cause a significant increase in both Aβ plaque accumulation and formation. Moreover, *APOE4* is involved in neuroinflammation and tau-mediated neurodegeneration, independently of Aβ pathology. *APOE4* carriers also have an increased risk of having ARIAs when undergoing anti-Aβ immunotherapy. ARIAs appear as regions of oedema or effusions (ARIA-E) in brain parenchyma or as haemorrhagic lesions (ARIA-H) in the form of cerebral microbleeds, hemosiderin deposits or intracerebral haemorrhage. The pathophysiology of ARIA is thought to be related to antibody-mediated breakdown of Aβ plaques, which results in the released Aβ being deposited in vessel walls.

The frequency of *APOE4* homozygosity within the Australian population has previously been observed to be lower than seen in international cohorts. Data from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing demonstrated the frequency of *APOE4* homozygosity to be 6.0% in patients with MCI and 5.6% in patients with severe AD.

The pivotal TB-2 trial enrolled patients who were 60–85 years of age (inclusive). The submission did not propose a lower (or upper) age limit in the proposed items. The justification provided in the submission was that clinical advice received from the sponsor's Advisory Board indicated that there were ethical concerns regarding an age criterion given the lack of available treatments, and that the proportion of eligible patients below the age of 60 years is only around 10%. The submission reported the prevalence of dementia in Australia as estimated by several sources. This has been summarised in Table 7. The submission noted that the variation in the estimates can be attributed to differences in the underlying data and definitions within these sources.

Table 7 The submission's estimation of dementia prevalence in Australia in 2023

Source	2023 calculated dementia population[a]		2023 calculated dementia prevalence per 1,000 people[a]	
	Age 60+ yrs	Age 65+ yrs	Age 60+ yrs	Age 65+ yrs
AIHW (2024)	405,627	382,280	66.8	83.8
ABS Census (2021)	190,251	185,194	31.3	40.6
NPS MedicineWise GPIR (2018-19)	130,713	-	21.5	-
SDAC (2018)[b]	-[b]	143,412	-[b]	31.5
DYNOPTA[b]	-[b]	618,615	-[b]	135.7

Notes: [a] Estimated total dementia population and prevalence per 1,000 people were calculated by applying the age and gender specific dementia prevalence rates reported in each data source to the Australian Bureau of Statistics estimated resident population, by age and sex at 30 June 2023. [b] Underlying studies report dementia prevalence rates from 65 years and above, dementia population/prevalence in a population 60+ not available.

Source: Table 1.7, page 20 of the submission

ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; DYNOPTA = Dynamic Analyses to Optimize Ageing; GPIR = Group Processes & Intergroup Relations; NPS = National Prescribing Service; SDAC= Survey of Disability, Ageing and Carers.

The submission has requested that Aβ testing for eligibility for treatment with donanemab be available for patients with early AD (MCI due to AD and mild AD) who have been confirmed as being *APOE4* heterozygous or non-carriers and Aβ-positive. The commentary considered that this population was fairly well described in the submission and is appropriate due to the high likelihood of having an ARIA event in patients who are homozygous for the *APOE4* allele.

The submission indicated that in 2025 there would be 60,000 to <70,000 patients diagnosed with early AD: 10,000 to <20,000 patients with MCI due to AD and 40,000 to <50,000 patients

with mild AD. Of these, the submission estimated that 20,000 to <30,000 (34.7%) patients would be tested for the presence of Aβ pathology after MRI results, MMSE scores and *APOE* genotyping were considered (30,000 to <40,000 patients would have been eligible for *APOE* genotyping). However, the commentary noted that these numbers were calculated using a prevalence of *APOE4* homozygosity of 10.9%. If, as stated above, the prevalence in Australia is lower at around 6%, the number of patients to be tested has been underestimated by the submission, with 20,000 to <30,000 patients being eligible for Aβ pathology testing. The population is also underestimated in the first year as no allowance has been made for patients previously diagnosed with MCI or early AD who may be eligible for treatment.

Currently, the diagnosis of AD is based on a detailed clinical consultation including patient history, cognitive assessments, medication review, blood tests and structural imaging (CT, MRI, ^{18}F-fluorodeoxyglucose (FDG)-PET). The proposed clinical management algorithm differs from the current clinical management algorithm by introducing several tests.

The submission proposed a blood-based PCR test for *APOE* genotyping for all patients with a clinical diagnosis of MCI due to AD or of mild AD who are potentially eligible for targeted treatment after MRI and other findings have been considered. Patients who are homozygous for the *APOE4* allele are at higher risk of developing ARIA adverse events from donanemab treatment and are excluded from treatment eligibility.

Patients who are not homozygous for *APOE4*, would then be eligible for either Aβ-PET or CSF AD biomarker testing. Patients testing positive to Aβ-PET or CSF AD biomarker testing would be eligible to receive donanemab treatment plus standard of care (SOC) whereas patients testing negative for Aβ pathology will need further specialist investigation to determine alternative causes of cognitive impairment.

Aβ-PET scanning uses small amounts of a radioactive substance (a radiotracer) to provide an image that visualises proteins associated with AD pathophysiology in the brains of affected individuals. Internationally, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved ^{18}F-Florbetaben (FBB; Neuraceq), ^{18}F-Florbetapir (FBP; Amyvid), and ^{18}F-Flutemetamol (FMM; Vizamyl) for amyloid imaging.

Aβ-PET scans are almost always performed with CT or MRI for accurate anatomic localisation of the pathology and for attenuation correction purposes. The submission stated that in their assessment of MSAC Application 1643, PASC noted that PET is never performed without CT in current clinical practice in Australia, except for rare cases in which PET/MRI is used.

The submission noted that in Australia, FBB, FBP, and FMM are currently commercially manufactured by one company, Cyclotek, for use in clinical trials in Australia and New Zealand. Cyclotek has also made FBB available through the Special Access Scheme for clinical use in Australia.

The submission also noted that Aβ-PET radiopharmaceuticals are produced by hospital nuclear medicine departments in Australia with onsite cyclotrons, and they do not require a Good Manufacturing Practice license (under Schedule 8 of the Therapeutic Goods Regulations 1990), which is mandatory for commercial companies.

The commentary noted that the half-lives of radiotracers used for Aβ-PET are comparatively short (e.g. the half-life of Fluorine-18 is 110 minutes). Therefore, these radiotracers need to be manufactured on site and administered to patients shortly following manufacture. Due to manufacturing sites requiring an onsite cyclotron, the health workforce and processes to manufacture the radiotracers, and the infrastructure to ensure that the radiotracers can be used shortly following manufacture, this may limit the number of facilities that are able to offer Aβ-PET

scans using radiotracers with short half-lives. This also affects the equitable access to the technology across the country.

Drug

The target population comprises patients with a clinical diagnosis of MCI due to AD or mild AD dementia that are subsequently confirmed as being *APOE4* heterozygous or non-carriers, Aβ-positive, and with no evidence on MRI brain of superficial siderosis or the presence of more than 2 microhaemorrhages. The requested target population in this submission aligns with the proposed TGA indication.

8. Comparator

Test

The main comparator for *APOE* genotyping followed by either Aβ-PET scanning or CSF AD biomarker testing in those who are not *APOE4* homozygous is 'no testing'. PASC also considered Aβ PET scanning a comparator for CSF AD biomarker testing to determine its diagnostic accuracy. The concordance between CSF testing and Aβ-PET was considered in the submission.

Drug

The submission nominated SOC as the main comparator. The commentary considered that it was appropriate. SOC encompasses non-pharmaceutical brain health optimisation strategies including exercise, nutrition, mentally challenging activities and social engagement, and symptomatic treatments. Symptomatic treatments for AD are limited to those focussed on providing symptomatic relief, including acetylcholinesterase inhibitors (AChEIs) and memantine. In Australia, AChEIs are PBS reimbursed for the treatment of mild to moderately severe AD and memantine for moderately severe AD. The commentary considered that as donanemab could be prescribed concurrently with SoC, the appropriate comparator would be no active therapy. In the key head-to-head TB-2 trial, placebo represents a proxy for no active therapy.

9. Summary of public consultation input

The organisations that submitted input were:

- Dementia Australia
- Cyclotek (Aust) Pty Ltd (Cyclotek)
- Australasian Association of Nuclear Medicine Specialists (AANMS)
- Roche Diagnostics Australia (Roche Diagnostics)
- Public Pathology Australia (PPA).

Level of support for public funding

All organisations that provided consultation input were supportive of the public funding of this application. However, input from the individuals was mixed. While 2 of the 3 individuals who provided input expressed support, the 3rd individual reported being unsure and considered that it would be better to wait until blood biomarkers of AD become available, as PET scanning might not be accessible for some individuals with dementia and CSF AD biomarker testing was invasive. The 3rd individual also did not support public funding and did not believe that there was efficient medical evidence to provide support. However, it was unclear if this individual was referring to the testing or donanemab treatment.

Comments on PICO

- Cyclotek noted the proposed eligibility criteria as appropriate. Roche Diagnostics was supportive of aligning CSF and/or PET confirmatory diagnosis with the population eligible for treatment with donanemab. The AANMS considered the proposed population as appropriate.
- Cyclotek considered Aβ-PET to be less invasive than CSF biomarker immunoassays, and that the use of Aβ-PET to determine access to PBS-subsidised donanemab aligned more closely with the studies and evidence relied on in the application. Cyclotek considered that the proposed eligible population captured those who would benefit from the proposed health technology, and did not consider it to be too broad.
- Roche Diagnostics noted that including CSF testing as an option for confirmatory diagnosis would be important for enabling broad access to testing for those eligible for donanemab treatment, stating that CSF testing could address access issues since samples could be collected in any appropriate treatment centre, which was important for those living in rural and regional areas.
- Cyclotek considered that the proposed approach to the delivery of the Aβ-PET services was appropriate, i.e., performed by nuclear medicine technologists under the supervision of accredited nuclear medicine providers, with results interpreted by accredited nuclear medicine providers, as consistent with current Australian clinical practice.
- Cyclotek noted that the proposed MBS item descriptor for Aβ-PET to determine eligibility had no cap while the proposed item to assess patient's response was limited to 3 per patients. Cyclotek noted that "in line with recent MSAC decision", lifetime scan limitations should not be imposed within the MBS item descriptor bur rather be determined on an individual basis. AANMS suggested an eligibility scan and follow-up scan limit of 1 and 3 over a 3-year period, respectively.
- Cyclotek agreed that a tracer-agnostic MBS item would allow for more equitable access to Aβ-PET tracers. Cyclotek disagreed that research Aβ-PET tracer, NAV4694, was the only Aβ-PET tracer currently available on Australia's west coast.
- Cyclotek noted that there might be concern regarding unequal access to Aβ-PET scan for regional and rural populations, as versus metropolitan areas. Cyclotek reported its commitment to leveraging a sublicensing model to produce Aβ-PET radiotracers and stated that it would subsidise the cost Aβ-PET tracers distributed to these areas.
- AANMS stated that Aβ-PET scans should be provided by a site serviced by accredited nuclear medicine specialists with expertise in interpretation of these PET scans.
- Cyclotek agreed that there were no appropriate comparators to test and monitor Aβ pathology, and that the accurate comparator for donanemab was standard of care. AANMS agreed that there was no direct comparator for Aβ scans and noted that fluorodeoxyglucose (FDG)-PET would not provide any information about amyloid burden. Roche Diagnostics noted the comparator as appropriate for the Australian setting, as there were no current specific diagnostic tests for AD in widespread utilisation.
- Cyclotek agreed that there was a more than reasonable level of certainty around the outcomes as proposed in the PICO set.
- Cyclotek agreed that MBS Items 61559 and 61560 were comparable MBS item numbers regarding Aβ-PET scans.
- AANMS noted that the general descriptor of PET for both eligibility and assessment of treatment response was appropriate, but suggested the inclusion of 'Centiloid score' in the interpretation of Aβ-PET scans to allow standardisation of the results.
- Cyclotek agreed that the MBS fee for proposed items should incorporate the current cost of performing and interpreting an ^{18}F-FDG study of the brain and substitute the cost of the ^{18}F-FDG radiotracer for the Aβ PET tracer. However, Cyclotek noted the fee for MBS item 61560 was an outlier and stated that most ^{18}F-FDG PET MBS item code fees more accurately reflect

the cost of the radiotracer, PET scan procedure, and results interpretation. AANMS supported the need for a reimbursement fee to cover the radiopharmaceutical itself, as well as an appropriate fee for service delivery. PPA noted it would be in a better position to advise on test costs in the near future.
- Roche Diagnostics noted the application did not currently include an item descriptor for *APOE4* genotyping, and suggested MSAC consider a cascade testing approach for *APOE4* status, noting that it would be willing to support MSAC in determining the appropriate fees for such testing.
- Roche Diagnostics noted the application did not currently include a specific fee for CSF confirmatory testing, stating that such testing was currently available in Australia on an out-of-pocket basis, which would likely be representative of an appropriate fee.

Perceived Advantages

- Three carers of individuals with AD noted the ability to diagnose symptoms of dementia is vitally important as it would provide the opportunity for early treatment by drugs designed to reduce or delay the onset of the disease.
- Dementia Australia noted these tests were essential to accurately determine eligibility and safety for donanemab, and to ensure that this emerging disease-modifying therapy would be used effectively and appropriately.
- Cyclotek noted there were currently no public funded services or technologies to assess Aβ pathology to determine access to publicly funded donanemab, and without public funding, there would be a significant financial toxicity associated with accessing these services and technologies.
- PPA described the proposed tests as appropriate to allow for the treatment of AD with PBS-subsidised donanemab.

Perceived Disadvantages

- A carer of an individual with AD expressed no concern regarding the tests proposed in this application.
- Another carer of an individual with AD noted the cost and invasive nature of testing, such as CSF sampling. The carer also noted that PET scanning was not widely accessible or tolerated by some people with dementia and expressed a preference for blood testing for AD if/when available.

Support for Implementation and Issues

- An individual with AD expressed the need for additional services, including counselling, a dietician, speech pathologist, and dermatologist. This individual also noted the need for transport for those living in regional areas.
- Two carers of individuals with AD considered that counselling after genetic testing is important to ensure that the patient and their family members understand the implications of a positive result.
- Dementia Australia considered that while new therapies for AD seemed to be promising, their success would depend on early diagnosis and access to treatment. Therefore, access to these tests would represent a positive step forward in making an early diagnosis and access to treatment possible in Australia as well as enable access to advanced care, financial and legal planning.
- Dementia Australia also considered that access and equity considerations were vital. The organisation stated that access to MBS-funded testing must be equally available to people living in rural and remote communities, Aboriginal and Torres Strait Islander peoples, culturally and linguistically diverse communities, and people with younger-onset dementia.

- Roche Diagnostics considered that the critical element for enabling access was to ensure that laboratories could deliver the testing in an economically sustainable model.
- AANMS reiterated the need for PET-scans to be provided by appropriately certified PET centres and qualified, reporting nuclear medicine specialists.
- PPA reported that due to the small volume of *APOE* genotype testing, its members would likely continue referring specimens to other pathology providers for this test.

10. Characteristics of the evidence base

The approach taken in the submission is to present evidence that has been linked to support the contention that targeting of Aβ plaques in the brain with donanemab will clear Aβ plaques in patients with confirmed pathological levels, leading to a clinical benefit.

The commentary considered that the populations and tests presented in the studies that formed the evidence base are mostly transferable across the linked evidence (Table 8).

Table 8 Summary of the linked evidence approach

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base	Used in modelled evaluation
Accuracy and performance of the test (cross-sectional accuracy)	4 NHMRC level III-2 studies provided DA evidence for FMM-Aβ-PET versus the clinical utility standard.	☒ k=4 n=602	High for patient selection, low for tests and timing	Not modelled.
	21 NHMRC level III-2 studies provided DA evidence for FMM-Aβ-PET and the clinical utility standard versus clinical diagnosis.	☒ k=21 n=1,377	Not assessed	Not modelled.
	11 NHMRC level III-3 studies provided concordance between CSF AD biomarker testing and Aβ-PET	☒ k=6 n=2,185	Low risk of bias	Not modelled.
	10 NHMRC level III-2 (k=8) and level III-3 (k=2) studies provided DA evidence the accuracy of *APOE* genotyping by PCR to detect the *APOE4* variant	☒ k=10 n=3,279	Not assessed	Not modelled.
	6 studies provided inter-rater reliability evidence on MRI detection of ARIA.	☒ k=6 n=455	Not assessed	Not modelled.
Prognostic evidence (longitudinal accuracy)	25 studies provided prognostic evidence. 1 SR 17 were NHMRC level II studies. 7 was NHMRC level III-3 studies	☒ k=25 n=9,928	Not assessed	Not modelled.
Change in patient management	2 studies provided evidence for a change in management 1 cross-sectional survey 1 prospective cohort study	☒ k=2 215 centres 99 patients	Not assessed	Not modelled.
Health outcomes (clinical utility)	No evidence presented	☐ k=0 n=0		
Predictive effect (treatment effect variation)	No evidence presented	☐ k=0 n=0		
Treatment effect (enriched)	1 key randomised controlled trial of drug vs placebo in patients that are test positive for	☒ k=1 n=1,736	Uncertain[a]	Modelled.

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base	Used in modelled evaluation
	Aβ pathology in both arms (TB-2)			
Other	20 studies provided DA evidence for plasma AD biomarker testing and CSF AD biomarker testing versus Aβ-PET	☒ k=20 n=6,060	Not assessed	Not modelled.

NHMRC levels of evidence: URL: https://www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf
Diagnostic accuracy levels of evidence: level III-1 = a study of test accuracy with an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation; level III-2 = a comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence; level III-3 = a diagnostic case-control study.
Prognostic studies: level II = a prospective cohort study; level III-3 = a retrospective cohort study; level IV = a case series, or cohort study of persons at different stages of disease.
[a]As assessed by the Commentary
Source: Table compiled by the evaluation group during evaluation.
Aβ-PET = amyloid-beta positron emission tomography; ARIA = amyloid-related imaging abnormalities; DA = diagnostic accuracy; CSF = cerebrospinal fluid; k=number of studies, MRI = magnetic resonance imaging; n=number of patients; NHMRC = National Health and Medical Research Council; SR = systematic review.

Overall, the commentary considered that the risk of bias in the TB-2 trial was uncertain. Although the trial investigators and other study personnel were blinded to allocation, the risk of functional unblinding from ARIAs, which are usually associated with anti-Aβ monoclonal antibodies, cannot be overcome particularly when patients could have learned they were on the intervention from experiencing treatment-related side effects. Such unblinding may bias responses on subjective cognitive and functional scales such as those used in the trial.

11. Comparative safety

Test

Adverse events from testing

Safety of Aβ-PET

The radiation exposure (effective whole-body dose) from Aβ-PET is about 4–7 millisieverts (mSv), which is within the range of commonly performed imaging studies, such as FDG-PET. Aβ-PET tracers offer a reasonable compromise between radiation exposure following ALARA (as low as reasonably achievable) principles, and image quality. The target organ (i.e., the organ with the highest absorbed radiation dose) for all three radiotracers is the gallbladder wall with an estimated mean absorbed radiation dose of 143, 287, and 137 μSv/MBq for FBP, FMM and FBB, respectively.[6]

Common adverse reactions from Aβ-PET scanning includes headache, injection site pain, injection/application site erythema, flushing, and increased blood pressure.

Safety of lumbar puncture for CSF AD biomarker testing

The submission stated that lumbar puncture is a safe procedure in older adults with or without cognitive impairment, with <1% of serious reported events needing specialist treatment. Risks of

[6] Minoshima S, Drzezga AE, Barthel H, et al. SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain 1.0. *J Nucl Med*. 2016 Aug;57(8):1316-22. doi: 10.2967/jnumed.116.174615. PMID: 27481605.

adverse events can be mitigated by considering the appropriate technical considerations when performing a lumbar puncture.

The most common associated AEs are headache, back pain, nausea/vomiting, and numbness of the legs.

The submission noted that the use of an atraumatic needle rather than a cutting-bevel needle, a needle with a gauge of >22, collecting the CSF sample passively, having the patient lay down, reducing the number of lumbar puncture attempts and collecting no more than 30 ml of CSF can all reduce the risk of post-lumbar puncture headache. The submission also noted that in rare cases, more severe presentation of symptoms may develop and that severe and persistent headaches may require treatment with an epidural blood patch.

Safety of MRI to detect ARIA

The submission did not discuss the safety of MRI. The commentary considered that as MRI does not expose the body to ionising radiation, it has a good safety profile. However, the commentary also considered that it is not without risks.

The radiofrequency energy used during the MRI scan can lead to heating of the body. The potential for heating is greater during long MRI examinations. Second degree burns are the most common adverse event for MRIs reported to the FDA[7]. Heating is thought to be a larger problem for people with tattoos, especially with new tattoos.

The powerful rapidly changing magnetic fields will attract metallic objects. Careful screening of people and objects entering the MR environment is critical to ensure nothing enters the magnet area that may become a projectile that may cause damage to the scanner or injury to the patient or medical professionals. The FDA has received reports on injuries caused by projectile events.

Patients with claustrophobia may find the inside of the MRI scanner to be uncomfortably small and may not be able to tolerate the scan. These patients, and those that cannot remain still will likely require anaesthesia to obtain a useful MRI result.

Safety of APOE genotyping

The commentary noted that *APOE* genotyping is performed on peripheral blood and sampling does not pose any serious risk to the patient. Due to the high accuracy of the *APOE* genotyping tests, the commentary considered that the likelihood of having a false negative or false positive test result is very low.

Drug

Adverse events from changes in management

Table 9 presented a summary of common key treatment-emergent adverse events (TEAEs) and ARIAs by treatment arm in the TB-2 trial.

[7] US Food and Drug Administration. MRI. Benefits and Risks. URL: https://www.fda.gov/radiation-emitting-products/mri-magnetic-resonance-imaging/benefits-and-risks last updated December 2017 [accessed 10 April 2024)

Table 9 Summary of TEAEs in the TB-2 trial

	Donanemab (N = 853), n/m (%)	Placebo (N = 874), n/m (%)
TEAEs	759 (89.0)	718 (82.2)
Treatment-related TEAEs[a]	410 (48.1)	173 (19.8)
TEAEs leading to treatment discontinuation	112 (13.1)	38 (4.3)
TEAEs leading to study discontinuation	69 (8.1)	32 (3.7)
ARIA-E	205 (24.0)	17 (1.9)
• Symptomatic ARIA-E	52 (6.1)	1 (0.1)
• Serious ARIA-E	13 (1.5)	0 (0)
• Treatment discontinuation	21 (2.5)	3 (0.3)
• *APOE4* heterozygous carriers	103/452 (22.8)	9/474 (1.9)
• *APOE4 non-carriers*	40/255 (15.7)	2/250 (0.8)
ARIA-H	268 (31.4)	119 (13.6)
• Serious ARIA-H	4 (0.5)	0 (0)
• Treatment discontinuation	20 (2.3)	6 (0.7)
• *APOE4* heterozygous carriers	146/452 (32.3)	57/474 (12.0)
• *APOE4 non-carriers*	48/255 (18.8)	28/250 (11.2)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)
Superficial siderosis of central nervous system	58 (6.8)	10 (1.1)
Dizziness	53 (6.2)	48 (5.5)
Arthralgia	49 (5.7)	42 (4.8)

Source: Table summarised during evaluation from Table 2.61, p203 of the submission.
APOE4 = apolipoprotein E allele 4; ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormalities-haemorrhage; N = number of patients in treatment group; n = number of patients with an event in each category; m = number of patients in each category; TEAE = treatment-emergent adverse event
Notes:
[a] TEAE was defined as an AE that emerged during treatment or within 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

The commentary noted that ARIA-E and ARIA-H events occurred more often in the donanemab arm than in the placebo arm. The frequency of ARIA-E and ARIA-H was more common in *APOE4* heterozygous carriers versus non-carriers in the donanemab group (22.8% and 32.3%, respectively, versus 15.7% and 18.8%). Patients who were homozygous for *APOE4* treated with donanemab had a higher incidence of ARIA in the brain, compared to heterozygotes and non-carriers.

12. Comparative effectiveness

Test

The data that are available in the submission for the relevant comparisons are outlined in Table 10. No evidence was provided on the performance of donanemab in a test negative population.

No evidence was provided in the submission on tau tests, either tau-PET or CSF tau, measurements to determine tau burden as a modulator of response to donanemab. The

commentary noted that in the TB-2 trial, patients were required to have tau-PET scans with evidence of pathologic tau deposition. The prespecified efficacy analyses were conducted in both the intermediate tau (low/medium tau) population and the overall tau population. However, the submission did not consider tau deposition status as a prerequisite for treatment with donanemab.

Table 10 Data availability to inform comparisons

Proposed test vs no test	No evidence presented	
Proposed test vs alternative test	Evidence presented for: FMM-Aβ-PET versus FBB- or FBP-Aβ-PET CSF versus Aβ-PET MRI for detection of ARIAs *APOE* PCR genotyping versus Sanger sequencing	
	Donanemab plus standard of care	Standard of care
Biomarker test positive	TRAILBLAZER-ALZ 2	TRAILBLAZER-ALZ 2
Biomarker test negative	No evidence presented	No evidence presented

Source: Table compiled during evaluation based on information from the submission.

The populations, tests and treatment regimens are transferrable across the linked evidence.

Overall, the commentary considered that the risk of bias in TRAILBLAZER-ALZ 2 (TB-2) trial was uncertain. Although the trial investigators and other study personnel were blinded to treatment allocation, the risk of functional unblinding from ARIAs, which are usually associated with anti-Aβ monoclonal antibodies, cannot be overcome particularly when patients could have learned they were on the intervention from experiencing treatment-related side effects. It is feasible that such unblinding may have biased responses on the subjective scales used in the trial, such as the Clinical Dementia Rating Sum of Boxes (CDR-SB), as well as assessments of activities of daily living, and safety.

Comparative accuracy/test performance

Clinical utility standard

Both FBB-Aβ-PET and FBP-Aβ-PET were used in the TB-2 trial to detect Aβ pathology. Thus, FBB- and/or FBP-Aβ-PET are considered to be the clinical utility standard.

Accuracy of FMM-Aβ-PET compared to FBB-Aβ-PET

The submission included four studies that showed a high level of concordance between Aβ-PET radiopharmaceuticals regardless of quantitative or qualitative interpretation.

Two of the four studies identified by the submission that directly compared the accuracy of FMM-Aβ-PET and FBB-Aβ-PET (the clinical utility standard) found that FMM had higher tracer retention in the striatum than FBB. A third study found high concordance between FMM-Aβ-PET and FBB-Aβ-PET and that all discordant results were FBB-negative and FMM-positive.

Three studies were identified during the evaluation that reported the accuracy of FMM-Aβ-PET compared with clinical diagnosis in terms of distinguishing patients with AD from other dementias or cognitively normal controls. A further 11 studies were identified that reported the accuracy of the clinical utility standard (FBB-Aβ-PET [n=2] or FBP-Aβ-PET [n=9]) compared with clinical diagnosis in determining the same outcome.

A bivariate hierarchical diagnostic accuracy meta-analysis (MA) using the 'midas' and 'metan' commands in STATA version 18.0 was conducted during the evaluation. The studies were divided into those reporting on visual assessment of Aβ-PET scans and those using quantitative methods

to evaluate the Aβ-PET scans. The results for the two radiotracer subgroups are shown in Figure 1 and Figure 2.

The commentary noted that at first glance visual assessment of FMM-Aβ-PET scans appears to be more accurate than visual assessment of the clinical utility standard when compared to clinical diagnosis (Figure 2A). However, this relies on a very small number of studies evaluating the accuracy of FMM-Aβ-PET. Additionally, as the tests used for a clinical diagnosis vary between studies and do not usually involve a test to directly detect the presence of Aβ pathology (imaging using MRI and possibly FDG-PET would likely be undertaken), it may lead to patients with non-AD pathology being classified as AD, and vice versa. As Aβ-PET scans do detect Aβ pathology, it is likely that they are more accurate in the diagnosis of AD. Thus, many of the "false negative" and "false positive" Aβ-PET results are likely to be true positive or true negative, with an inaccurate clinical diagnosis. Clinical diagnosis in this instance is an imperfect reference standard. This partially explains the difference in sensitivity and specificity between many of the included studies. The randomly selected AD patients and cognitively normal controls would vary in the proportion who had Aβ pathology. The age of the cognitively normal controls would also influence the proportion with Aβ pathology (these patients would be considered false positive). The prevalence of Aβ pathology among participants with normal cognition increased from 10% at age 50 years to 44% at age 90 years. Thus, studies with outlier results were further investigated and excluded from the MA. This improved the sensitivity and specificity of the clinical utility standard using visual assessment of Aβ pathology, as shown in Figure 1B, but has little effect on the sensitivity and specificity for quantitative assessment of Aβ-PET scans.

Overall, the commentary considered that Aβ-PET using FMM, FBB or FBP radiotracers showed relatively high sensitivity and specificity and provide a reliable test for determining Aβ pathology.

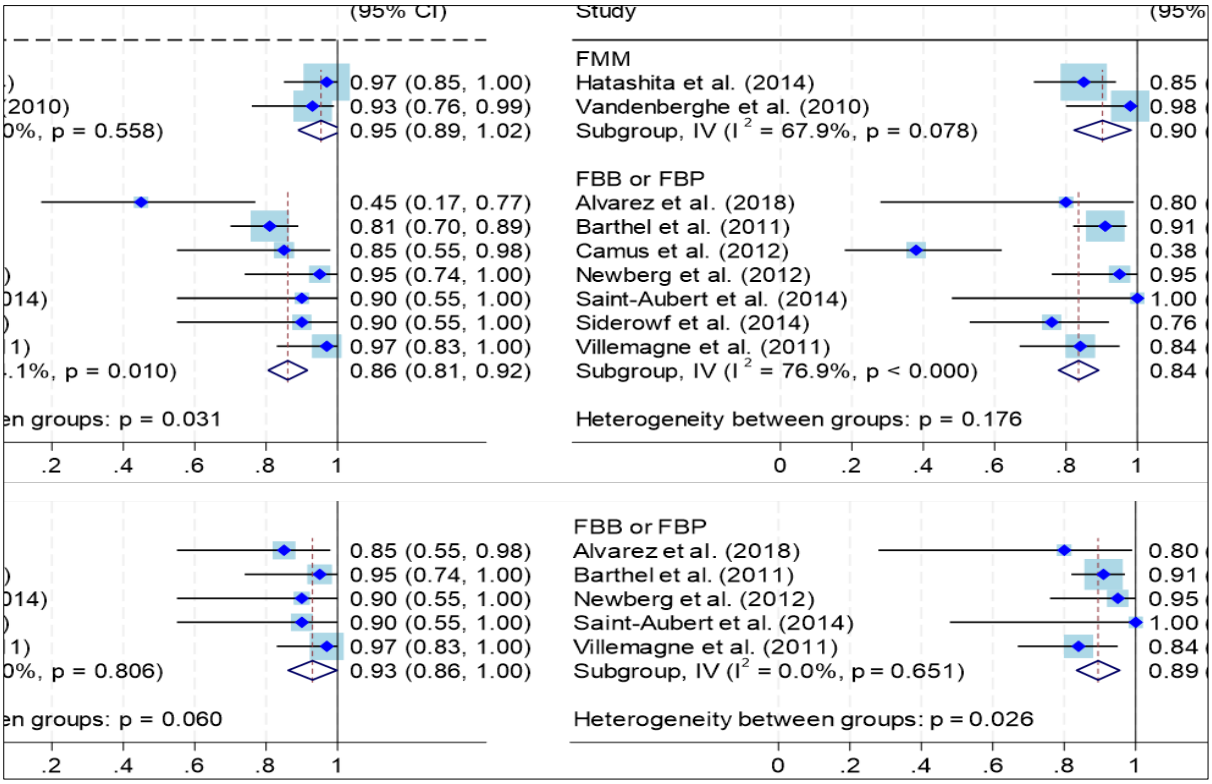

Figure 1 The accuracy of visual assessment of Aβ-PET scans in detecting AD compared to clinical diagnosis

(A) Meta-analysis with all included studies, (B) Meta-analysis of the clinical utility standard where the two outlier studies for sensitivity and specificity have been excluded, as described in the text below.

Aβ = amyloid-beta; CI = confidence interval; FBB = ^{18}F-florbetaben; FBP = ^{18}F-florbetapir; FMM = ^{18}F-flutemetamol; PET = positron emission tomography

Source: constructed during the evaluation

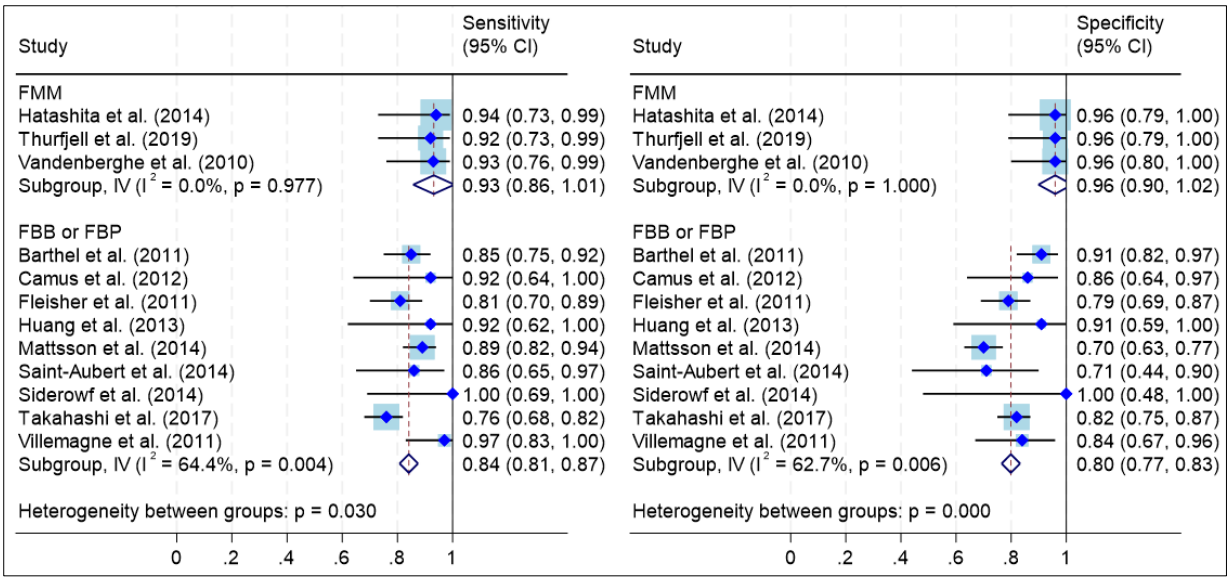

Figure 2 The accuracy of quantitative SUVr assessment of Aβ-PET scans in detecting AD compared to clinical diagnosis

Aβ = amyloid-beta; CI = confidence interval; FBB = ^{18}F-florbetaben; FBP = ^{18}F-florbetapir; FMM = ^{18}F-flutemetamol; PET = positron emission tomography; SUVr = standard uptake value ratios

Source: constructed during the evaluation

CSF AD biomarker testing

Eleven studies that directly compared the concordance of CSF AD biomarker testing with the clinical utility standard (FBB- or FBP-Aβ-PET) were included in the analysis conducted during the evaluation.

A bivariate hierarchical diagnostic accuracy MA using the 'midas' and 'metan' commands in STATA version 18.0 of the extracted 2x2 data was conducted during the evaluation when at least four studies were available. If insufficient data were available for MA the median and range for the positive percent agreement (PPA) and negative percent agreement (NPA) were calculated. The pooled statistics are shown in Table 11.

Table 11 Pooled accuracy of CSF AD biomarker testing compared with Aβ-PET

CSF AD biomarker (cut-off range)	PPA pooled (95% CI) or median (range)	NPA pooled (95% CI) or median (range)
Aβ42 (192–976.6 pg/ml)	V: 87% (95% CI 72, 95), k=7 Q: 83% (95% CI 70, 91), k=6	V: 79% (95% CI 68, 91), k=7 Q: 82% (95% CI 68. 91), k=6
p-tau181 (61.8–88 pg/ml)	V: 66% (95% CI 57, 74), k=4 Q: 80% (95% CI 67, 89), k=1	V: 82% (95% CI 73, 89), k=4 Q: 83% (95% CI 66. 93), k=1
t-tau (348–539 pg/ml)	V: 76% (95% CI 70, 81), k=5 Q: 75% (95% CI 62, 85), k=1	V: 80% (95% CI 71, 86), k=5 Q: 83% (95% CI 66. 93), k=1
Aβ42/Aβ40 ratio (0.062-0.088)	V: 98% (range 82-100), k=3 Q: 83% (range 77-88), k=2	V: 72% (range 56-82), k=3 Q: 80% (range 77. 82), k=2
p-tau181/Aβ42 ratio (0.0103–0.064)	V: 92% (range 80-92), k=3 Q: 89% (range 85-93), k=2	V: 91% (range 86-91), k=3 Q: 87% (range 80-94), k=2
t-tau/Aβ42 ratio (0.27-0.641) Aβ42/t-tau ratio (2.153)	V: 93% (95% CI 87, 96), k=6 Q: 81% (range 81-82), k=3	V: 87% (95% CI 80, 92), k=6 Q: 94% (range 83-100), k=3

Aβ = amyloid-beta; Aβ40 = Aβ1-40; Aβ42 = Aβ1-42; AUC = area under the curve; CI = confidence interval; CSF = cerebrospinal fluid; k = number of studies; NPA = negative percent agreement; PET = positron emission tomography; PPA = positive percent agreement; p-tau = phosphorylated tau; Q = quantitative; ROC = receiver operating characteristic; t-tau = total tau; V = visual

Source: constructed during the evaluation

The proportion of discordant results between CSF AD biomarker tests and Aβ-PET scans was higher for single CSF AD biomarkers than for most ratio combinations. All three biomarker ratio combinations included Aβ42 and all had an improved PPA over Aβ42 alone (92–98% versus 87% when compared to visual assessment of Aβ scans). The NPA for p-tau181/Aβ42 and t-tau/Aβ42 were higher compared with Aβ42 alone (91% and 87% versus 79%), but not the Aβ42/Aβ40 ratio (72% versus 79%), when compared to visual assessment of Aβ scans. When the accuracy of the CSF AD biomarkers was compared to quantitative assessment of Aβ scans, the PPA and NPA for single biomarkers were either similar or lower than for the biomarker ratios (75-83% versus 81-89% for PPA and 82-83% versus 80-94% for NPA).

The commentary noted that the Elecsys® CSF assays, which are listed on the ARTG for use in Australia, provide results for pTau/Aβ42 and tTau/Aβ42 ratios. A result above the cut-off of 0.023 and 0.28, respectively, is consistent with a positive result.

The commentary considered that there are several reasons why CSF Aβ levels and Aβ-PET may be discordant. Firstly, the two tests measure different species of Aβ. Aβ-PET detects aggregated forms of Aβ, whereas CSF immunoassays measure the concentration of Aβ42 peptide monomers in the CSF. Also, both tests are subject to errors and variability. The CSF AD biomarker test may be affected by factors related to collection and storage procedures, as well as different protocols and techniques, leading to variability in the measured concentrations of CSF AD biomarkers. Aβ-PET results can be affected by differences in radiotracer characteristics, subject movement, or Aβ threshold selection, as well as inter-rater variability.

The commentary noted that when comparing visual assessment of Aβ scans with a ratio of two CSF AD biomarkers, 2-7% of Aβ-PET positive tests will be CSF Aβ42 negative (i.e. 'false negative') and 9-28% of Aβ-PET negative tests will be CSF Aβ42 positive (i.e. 'false positive'). When quantitative assessment of Aβ scans is compared with a ratio of two CSF AD biomarkers, 11-19% will be 'false negative' and 6-20% will be 'false positive'. The studies included in the assessment of the concordance between Aβ-PET and CSF AD biomarker testing did not aid in determining which would be more accurate compared to a definitive diagnosis (e.g. using the gold standard of Aβ pathology by autopsy).

The commentary noted that a systematic review of diagnostic test accuracy in AD found that CSF AD biomarker testing had a pooled sensitivity of 89.4% (95% CI 84.4, 94.8; k=3) and a pooled specificity of 70.5% (95% CI 59.6, 81.4; k=3) when compared to neuropathology at autopsy. A meta-analysis conducted during evaluation of 5 studies comparing the accuracy of Aβ-PET with autopsy found that the pooled sensitivity was 93% (95% CI 90, 96) and the pooled specificity was 91% (95% CI 86. 94).

Thus, the commentary considered that CSF AD biomarker testing is likely to result in a higher proportion of patients with false negative results who will miss out on treatment with donanemab and false positive results, who will receive treatment with donanemab with no benefit, when compared with Aβ-PET scanning.

APOE genotyping by PCR

There was no indication in the submission as to what type of polymerase chain reaction (PCR)-based *APOE* genotyping methods were used in Australian diagnostic laboratories. Real-time (RT) PCR-based techniques, including high resolution melt, TaqMan probe and Fluorescent Resonance Energy Transfer (FRET) methods are currently the most relevant methods for diagnostic genotyping.

Ten studies that were identified in a rapid non-systematic literature search during evaluation were included to determine the accuracy of PCR-based methods in detecting *APOE* ε2, ε3 and ε4

alleles. These studies used several different *APOE* genotyping methods. Overall, the various PCR-based genotyping methods are highly concordant and highly accurate compared to Sanger sequencing (94-100%), which is considered to be the gold reference standard for determining the *APOE* genotype and also has a PCR component.

MRI monitoring for ARIA

No evidence was provided by the submission on the accuracy of the use of MRI to monitor for ARIA events. A rapid non-systematic literature search during the evaluation identified seven articles that were included. Only one study provided any evidence for ARIA-H.

MRI has been found to be useful for monitoring the increased occurrence of ARIAs in MCI and AD patients receiving anti-Aβ therapies. The trials that have used anti-Aβ antibodies for Aβ clearance and subsequently monitored patients for ARIAs have used 2D T2-FLAIR MRI sequences for the detection and management of ARIA-E and 2D T2*-GRE MRI sequences for ARIA-H. These MRI sequences have been reported to be the most effective for this purpose.

The inter-rater agreement for the rating of ARIA-E severity was high for all rating scales included in the studies. This suggests that MRI is a reliable method for determining the presence of ARIA-E. Additionally, there was high concordance between rating scales and the Barkhof Grand Total Scale (BGTS) rating scale was highly concordant with the known status of the patients whose images were examined. The study that investigated the accuracy of MRI in detecting both ARIA-E and ARIA-H events concluded that the concordance between raters was good (0.6-0.9), and diagnosis was significantly better when using the AI-based assistive software.

Prognostic evidence

The data from 25 studies reporting on the prognostic effect of the Aβ biomarker, detected by either Aβ-PET or by CSF AD biomarker testing was assessed during the evaluation.

Of the eight studies that investigated the prognostic value of Aβ burden at baseline (detected by Aβ-PET) in predicting cognitive decline from MCI to AD, seven found some significant association. The eighth study reported that the sensitivity and specificity of Aβ-PET for differentiation between stable MCI and conversion of MCI to AD was 66.7% and 60%, respectively, but did not comment on whether this showed a statistically significant ability to identify MCI patients likely to convert to AD. Two studies investigated whether there was any association between conversion to AD and longitudinal Aβ burden changes but found no association.

Of the 17 studies reporting on the prognostic effect of CSF AD biomarkers, 13 reported on an association between the CSF AD biomarker concentrations and cognitive decline in MCI patients, leading to progression to AD. Eight found Aβ42 levels were predictive, and eight found t-tau and/or p-tau levels to be predictive. Of the studies that investigated the ability of CSF AD biomarker ratios to predict progression to AD, 4/4 and 3/3 studies found t-tau/Aβ42 and p-tau/Aβ42 ratios, respectively, to be predictive. However, only 1 out of 3 studies found Aβ42/Aβ40 ratios to be predictive. Two studies found no association between CSF AD biomarkers and time to conversion from MCI to AD. In contrast, three other studies found some association between biomarker levels and the rate of cognitive impairment.

Of the 25 studies included as providing prognostic evidence (24 identified during the evaluation), 20 (80%) found that Aβ burden, as determined by either Aβ-PET or CSF Aβ42 concentration, predicted progression to AD in patients with subjective cognitive decline or MCI. Assuming these associations are reliable, the commentary considered that this suggests that Aβ burden is prognostic of cognitive decline over time.

Predictive evidence

No studies were identified by the submission, or during the evaluation, that investigated the long-term effect of Aβ immune therapy (active or passive) in patients who have detectable Aβ pathology compared to those who do not.

Change in management in practice

This submission proposed a change in clinical management for patients with early AD, who have Aβ pathology confirmed by Aβ-PET or CSF AD biomarker testing.

The submission suggested that patients who do not have Aβ pathology detected by Aβ-PET or CSF AD biomarker testing will not have a change in management and will receive SoC, as per the current clinical management algorithm.

The commentary considered that this assumption was reasonable, although there may be some potential for changes to treatment options beyond donanemab treatment.

During the evaluation, two studies were identified that discussed a change in management of up to 40% of patients diagnosed with subjective cognitive decline (SCD), MCI or AD after CSF AD biomarker testing or Aβ-PET scanning. The change in management did not involve anti-Aβ therapies but included the initiation of other medications, such as cholinesterase inhibitors and memantine, or non-pharmacological treatments, such as occupational therapy.

The commentary considered that these studies indicate that there are other clinical uses for both Aβ-PET and CSF AD biomarker testing that could potentially lead to leakage, where the proposed MBS items may be used for purposes other than determining eligibility to donanemab.

Drug

A summary of the comparative benefits and harms for donanemab versus placebo at 18 months in the pivotal TB-2 trial was presented in Table 12.

Table 12 TB-2: Summary of comparative benefits and harms for donanemab (700 mg Q4W for the first 3 doses, followed thereafter by 1,400 mg Q4W) compared with placebo (overall population) – 76 weeks follow-up

Outcome	Donanemab	Placebo
Benefits (Evaluable Efficacy Set)		
Primary outcome of iADRS[a] change from baseline at 76 weeks	**N=583**	**N=653**
Mean change from baseline	-10.19	-13.11
Difference in mean change donanemab minus placebo (95% CI)	2.92 (1.51, 4.33) p<0.001	
% reduction (slowing) in disease decline, donanemab vs. placebo (delay in decline)	22.3% (1.38 months delay)	
Secondary outcome of CDR-SB change from baseline at 76 weeks	**N=598**	**N=672**
Mean change from baseline	1.66	2.33
Difference in mean change donanemab minus placebo (95% CI)	-0.67 (-0.92, -0.43)	
% reduction (slowing) in disease decline, donanemab vs. placebo (delay in decline)	28.9% (5.44 months delay)	
CDR-G[b] Shift from baseline (progression to a later stage) (added by commentary during evaluation)		
From 0.5 to 1 (MCI to Mild AD Dementia), n/N (%)	**N=502** 134/502 (27%)	**N=521** 202/521 (39%)
Difference donanemab minus placebo	-12.1%	
From 1 to 2 (Mild AD Dementia to Moderate AD Dementia), n/N (%)	**N=292** 51/292 (17.5%)	**N=302** 82/302 (27.2%)
Difference donanemab minus placebo	-9.7%	

Harms (Safety Analysis Set)					
TEAEs	**Donanemab n/N**	**Placebo n/N**	**Event rate/100 patients**		**Risk difference**
			Donanemab	**Placebo**	
ARIA-E, Overall population	205/853	18/874	24.0	2.1	21.9
ARIA-E, TGA population [c]	139/689	11/692	20.2	1.6	18.6
ARIA-H, Overall population	268/853	119/874	31.4	13.6	17.8
ARIA-H, TGA population [c]	184/689	75/692	26.7	10.8	15.9
Microhaemorrhage [c]	159/689	72/692	23.1	10.4	12.7
Infusion-related reactions	74/853	4/874	8.7	0.5	8.2

Source: Sections 2.D.5 and 2D.6 of the submission, the TB-2 Clinical Study Report (ARIA safety data by *APOE4* carrier status), Zimmer et al (2024) (CDR-G shifts), and the FDA Clinical Review of donanemab (Infusion-related reactions in TB-2)

AD=Alzheimer disease; ADAS-Cog13=Alzheimer Disease Assessment Scale (Cognitive subscale); ADCS-iADL=Alzheimer Disease Cooperative Study – Instrumental Activities; *APOE4*=apolipoprotein epsilon 4; CDR-SB=Clinical Dementia Rating scale Sum of Boxes (values range from 0 to 18, with higher scores indicating greater impairment); CDR-G=Clinical Dementia Rating-Global score; CI=confidence interval; iADRS=Integrated Alzheimer Disease Rating Scale; MCI=Mild Cognitive Impairment

[a]The iADRS assesses the impact of cognitive loss on the ability to conduct everyday activities and provides a measure of global AD severity across the AD continuum as a single summary score. The composite score comprises two underlying domains: cognitive ability and functional ability. The actual scales administered to participants in the trial were the ADAS Cog13 and the ADCS-ADL.
Lower scores on the iADRS indicate greater impairment; iADRS scores range from 0 to 144. All items of the ADAS-Cog13 and ADCS-iADL are included without additional weighting of items.

[b]CDR-G Shift represents change in CDR-G from baseline at two consecutive visits. Only shifts from MCI to Mild AD and from Mild AD to Moderate AD are included in table. Other shifts were imprecise.

[c] Based on Safety MRI or TEAE Cluster, Safety Analysis Set Excluding ApoE homozygotes or ApoE missing, baseline or missing superficial siderosis, ≥3 or missing microhaemorrhage (pp8-9, Attachment 3.4_Economic model TB-2 revised TGA population outputs of the submission).

The therapeutic conclusion in the submission was that in patients with early symptomatic AD, (excluding patients who are *APOE4* homozygous and patients with an MRI brain findings of baseline presence of superficial siderosis and more than 2 microhaemorrhages), amyloid testing (Aβ PET or CSF AD protein biomarker testing) followed by treatment with donanemab + SoC in patients with evidence of Aβ pathology is superior to no amyloid testing and treatment with SOC in terms of effectiveness.

MSAC noted the commentary considered that based on the effectiveness data, in patients with a clinical diagnosis of MCI due to AD or mild AD who were not *APOE4* homozygous and who did not have MRI brain findings of superficial siderosis and more than 2 microhemorrhages, donanemab ± SoC was statistically significantly superior to no active therapy ± SoC in the rate of decline (slowing) of clinical disease progression in both cognitive and functional scales at 76 weeks. However, the clinical significance of this treatment effect is uncertain.

13. Economic evaluation

The submission presented a modelled economic evaluation based on the treatment effect observed in the TB-2 trial which compared donanemab treatment to SOC in patients with early AD with a positive Aβ biomarker test and who were not *APOE4* homozygous. The type of economic evaluation presented was a cost-utility analysis.

Method

Table 13 Summary of testing key inputs and rationale in the submission's economic model

Component	Summary
Comparison	Donanemab with amyloid and *APOE4* testing versus SOC. This was reasonable.
Outcomes	QALYs.
Time horizon	Lifetime (26 years) in the model base case (versus 18 months in the key trial). A lifetime extrapolation is reasonable however a shorter time horizon was adequate to capture the differences between the arms. The data was reasonably immature, the majority of the modelled benefit was accrued during the extrapolated period.
Test parameters	Patients enter the model at the point of treatment and each patient incurs the testing costs associated with the number required to identify one treated patient with donanemab. This was reasonable as testing costs for all patients considered for the medicine are included in the model.
Implications of false positive and false negative results	Not considered in the economic evaluation. While this was reasonable for PET scans (as this was used in the trial and would have the same performance in practice), CSF assays which was not used in the trial and can be used in practice, have a 6 – 28% false positive rate when compared to PET. The submission has not considered that in clinical practice a proportion of patients with false positive CSF assays would be eligible for donanemab treatment which would affect the overall treatment effect of donanemab.
Tests required for access to PBS subsidised donanemab	• PET or CSF test (50% of patients each) for 1.18 patients (the number of treated patients versus tested patients). Although the distribution of patients testing through PET or CSF was uncertain, this was reasonable. • *APOE4* test for 1.57 patients (the number of treated patients versus tested patients). The source behind the number of treated versus tested patients was not provided. • MRI brain scan for 18% of patients. Assuming that the remaining patients would have an MRI brain as part of usual clinical diagnosis. However, this does not account for the proportion of patients who would fail the pre-treatment MRI.
Testing costs	• The amyloid PET scan was assumed to cost $2,300, consisting of the cost of the proposed MBS item descriptor ($2,200) and MBS 61505 ($100) for a CT scan alongside a PET scan. • The cost of the CSF test was assumed to be $750, consisting of the cost of the proposed MBS item descriptor ($400), MBS 56223 ($264) for CT of the spinal region and MBS 39000 ($86) for a lumbar puncture. • *APOE4* testing was assumed to be $160, consisting of the cost *APOE4* testing as proposed in the MBS item descriptor ($154) and MBS item 73928 ($5.95) for blood collection. • MRI costs were based on the pre-existing MBS item 63004, MRI of the head, $441. These costs were reasonable however the submission did not consider anaesthesia that may be required for some patients during testing, however this is unlikely to have an effect on the economic model.
Amyloid monitoring	The model assumes that 40% of patients would have their amyloid levels monitored through a PET scan at 6 and 12 months and if amyloid clearance were achieved, they would cease treatment. The other 60% of patients were assumed to be treated until the maximum treatment duration (18 months). This distribution is substantially uncertain, but affects only the costs in the economic model as patients who cease treatment early (32% and 37% of screened patients at 6 and 12 months, respectively, based on the TB-2 trial) have the same treatment effect waning assumptions incorporated in the model as those who complete the full treatment course.

Source: *Constructed during the evaluation from the* "3.3_Donanemab cost effectiveness model" attachment provided with the submission.
AD = Alzheimer Disease; *APOE* = Apolipoprotein E gene; CSF = cerebrospinal fluid; MBS = Medicare Benefits Schedule; MRI = magnetic resonance imaging; PET = Positron Emission Tomography; QALY = qualify-adjusted life year; SOC = Standard of Care.

The economic model adopted a Markov model structure with two settings (community and institutional) and four health states (MCI due to AD, mild, moderate and severe AD) in each setting based on AD disease severity (as per Clinical Dementia Rating – Sum of Boxes [CDR-SB]) and a dead health state. Patients entered the model at the point of treatment and testing costs associated with the number of patients tested were applied to each patient upon model entry. The commentary considered that this was reasonable.

No consideration was given to the likelihood of false-negative and false positive results. The commentary considered that while this was reasonable for PET scans (as this was used in the trial and would have the same performance in practice), CSF assays which were not used in the trial and may be used in practice, have a 6 – 28% false positive rate when compared to PET scans (see Comparative accuracy/test performance). The submission had not considered that in clinical practice a proportion of patients with false positive CSF assays would be eligible for donanemab treatment which would affect the overall treatment effect of donanemab. The impact of this was not able to be explored during the evaluation due to the structure of the economic model. MSAC considered that the economic evaluation should consider the whole population, both tested and treated populations, especially in the context of two proposed alternative tests for Aβ pathology which might have discordant results to determine access to a drug and the pivotal TB2 trial used only one of the tests. MSAC considered that the economic model should incorporate the downstream impact of false positive (e.g., potential harms from unnecessary donanemab treatment and associated monitoring) and false negative test results (e.g., not eligible to donanemab treatment).

Three tests are required for patients who already have an MCI or mild AD diagnosis before they can be treated with donanemab: a pre-treatment MRI, *APOE4* and Aβ tests. Patients must test positive for Aβ through either a PET scan or CSF test. The submission cited the Australian Dementia Network Registry 2022 Annual Report and indicates that 61% of patients with MCI due to AD and 91% of patients with mild AD are Aβ positive.[8] The commentary noted that these values were not able to be verified from the report. The calculated rate of Aβ positivity (weighted by the proportion of patients with MCI due to AD and mild AD at model entry) was 85% and was relatively similar to the Aβ positivity rate during TB-2 screening (75% with 25% of patients being excluded due to negative amyloid on PET). The amyloid positivity rate from the trial was tested in sensitivity analyses (see Table 17).

The submission assumed a prevalence rate of non-*APOE4* homozygotes of 64% in the economic analysis, hence 1.57 patients would need to be tested to identify one treatment eligible patient. The source of this estimate was not provided in the submission. The commentary noted that the financial analysis applied a prevalence rate of 89% for non-homozygotes (11% for homozygotes) whereas the proportion of non-homozygotes in the TB-2 trial was 71%. These alternative prevalence rates were tested in sensitivity analyses; however, the model was not sensitive to these alternative values.

As per the PBS restriction, a pre-treatment MRI is needed rule out haemorrhage or ARIA events. Based on a commissioned analysis of AD patients in Australia conducted by Ipsos, the submission estimated that 82% of patients would have an MRI upon diagnosis (regardless of donanemab treatment), hence the submission has only costed pre-treatment MRIs for 18% of donanemab patients. The commentary considered that this was reasonable. However, this approach assumed that all patients would pass the pre-treatment MRI. In the financial analysis, 89% of patients are modelled to pass the pre-treatment MRI. This proportion should be used to calculate the number of pre-treatment MRI scans per treated patient (1.12) and then applied to the 18% of patients who undergo the pre-treatment MRI. The model was not sensitive to small changes in the number of scans per patient.

The submission has not considered that testing for PBS subsidised donanemab may occur in a sequential testing approach. As per the proposed clinical management algorithm (see Change in

[8] Australian Dementia Network Registry (2023), 2022 Annual Report. https://australiandementianetwork.org.au/wp-content/uploads/2023/05/ADNeT22_Report_F1_Web.pdf.

management in practice), MRI scans would be performed first, followed by *APOE4* and then Aβ testing. This would mean the number of patients who undergo MRI scans per treated patient would need to include the proportion of patients passing *APOE4* and Aβ testing and the number of patients who undergo *APOE4* would need to include the proportion of patients passing Aβ tests. The impact of sequential testing on the overall cost of testing required to establish eligibility for donanemab was included in sensitivity analyses.

As mentioned above, Aβ biomarker testing included either a CSF test or PET scan. The submission assumed that an even distribution of patients would initially test with either CSF or PET (i.e. 50% each). The commentary noted that this distribution, while uncertain, was not a significant model driver. However, the submission did not consider if patients who receive a negative CSF result would re-test again with PET. This was also tested in sensitivity analyses.

The amyloid PET scan was assumed to cost $2,300, consisting of the cost of the proposed MBS item descriptor ($2,200) and MBS 61505 ($100) for a CT scan alongside a PET scan. The cost of the CSF test was assumed to be $750, consisting of the cost of the proposed MBS item descriptor ($400), MBS 56223 ($264) for CT of the spinal region and MBS 39000 ($86) for a lumbar puncture. *APOE4* testing was assumed to be $160, consisting of the cost *APOE4* testing as proposed in the MBS item descriptor ($154) and MBS item 73928 ($6) for blood collection. MRI costs were based on the pre-existing MBS item 63004, MRI of the head, $441. These costs were reasonable.

A summary of the proportion of tested and treated patients and associated diagnostic costs per treated patient for donanemab is presented in Table 14.

Table 14 Number of patients undergo diagnostic testing for donanemab eligibility and associated costs

Test	Base case pass rate	Proportion of treated patients	Cost per test applied in model	Number of tests per treated patient[a]
Amyloid – PET	85%[b]	50%[c]	$2,300.00	1.18
Amyloid – CSF		50%[c]	$749.50	
APOE4	64%[b]	100%	$159.95	1.57
Pre-treatment MRI	100%	18%[d]	$441.45	1.00
Total diagnostic cost per treated patient				**$2,129.92**

Source: *Constructed during the evaluation from the* "3.3_Donanemab cost effectiveness model" attachment provided with the submission.
AD = Alzheimer Disease; *APOE* = Apolipoprotein E gene; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] 1 / base case pass rate

[b] *These values were not able to be verified during the evaluation.*

[c] The submission assumed 50% of patients would test for amyloid through PET and 50% would test through CSF.

[d] The submission assumed only 18% of patients would need an MRI prior to treatment as the remaining patients would have received one upon diagnosis of MCI or AD.

As indicated in the proposed PBS criteria, donanemab has a treat-to-clear strategy where patients' amyloid levels are monitored at 6 and 12 months and treatment ceased if there is amyloid clearance defined as an Aβ-PET level of <24.1 CL. Patients who do not achieve amyloid clearance are assumed to complete the full 18-month treatment course. This strategy was employed in the TB-2 trial for all patients. However, in the economic model the submission assumed that only 40% of donanemab patients would undergo this strategy through PET scans (costing $2,300 per scan). The other 60% of patients were assumed to be treated until the maximum treatment duration (18 months). The commentary considered that this distribution was substantially uncertain in the Australian setting, but affected only the costs in the economic model as patients who ceased treatment early (32% and 37% of screened patients at 6 and 12 months, respectively, based on the TB-2 trial) had the same treatment effect waning assumptions incorporated in the model as those who complete the full treatment course. If the availability of PET scans in Australia cannot accommodate such a large proportion of patients

having 6 and 12 monthly PET scans while on donanemab treatment, then some of these patients may receive longer donanemab treatment than is necessary.

Consistent with the TB-2 trial and the draft PI, the submission's economic model also includes two MRI scans for each ARIA adverse events (AEs) while on treatment for donanemab. The commentary considered that this was reasonable, the incidence of ARIAs was sourced from the TB-2 trial and applied as a once-off cost upon model entry.

Results of the economic model

The submission presented a three-stepped economic analysis. However, the inclusion of modelled parameters between the steps was not described. Accordingly, the evaluation has presented a more transparent stepped analysis, see Table 15. As the institutionalisation rates were substantially uncertain, these have been incorporated into the last step of the analysis along with carer QALYs (which fall outside the scope of a base case analysis) to allow their effect to be clearly observed. Incorporation of institutionalisation reduced the incremental costs by $REDACTED.

Table 15 Results of the stepped economic evaluation, conducted during the evaluation

Step and component	Donanemab	SOC	Increment
Step 1: Trial based outcomes and costs (18-month time horizon)			
Costs[a]	$REDACTED	$619	$REDACTED
% of patients with MCI due to AD[b]	73%	61%	12%
% of patients with mild AD[c]	83%	73%	10%
Incremental cost per MCI progression avoided			$REDACTED
Incremental cost per mild progression avoided			$REDACTED
Step 2: Time horizon extended to 30 years and adding disease management costs			
Costs	$REDACTED	$103,238	$REDACTED
LYs gained	10.77	10.75	0.02
Incremental cost/extra LYG gained			$REDACTED [1]
Step 3: Transformation to QALYs, 5% p.a. discounting			
Costs	$REDACTED	$70,298	$REDACTED
QALY gained	4.48	4.14	0.34
Incremental cost/extra QALY gained			$REDACTED [2]
Step 4: Incorporation of institutionalisation costs and carer QALYs			
Costs	$REDACTED	$414,477	$REDACTED
QALY gained	3.70	3.28	0.42
Incremental cost/extra QALY gained (base case)			**$REDACTED [3]**

Source: Constructed during the evaluation from the "3.3_Donanemab cost effectiveness model" attachment provided with the submission.
AD = Alzheimer Disease; LYs = life years; MCI = mild cognitive impairment; p.a. = per annum; QALYs = quality adjusted life years; SOC = standard of care.

[a] Costs include donanemab diagnostic, acquisition, administration and monitoring costs, symptomatic treatment and adverse event costs.

[b] Proportion of MCI due to AD patients at baseline remaining as MCI due to AD at the end of the 18-month trial period as per CDR score reported in Zimmer et al (2024).[9]

[c] Proportion of mild AD patients at baseline remaining as mild AD at the end of the 18-month trial period as per CDR score reported in Zimmer et al. (2024).

The redacted values correspond to the following ranges:

[1] >$1,055,000

[2] $155,000 to <$255,000

[3] $35,000 to <$45,000[9]

[9] Zimmer, JA (2024). Insights from TRAILBLAZER-ALZ 2 (Donanemab): Clinical Efficacy. Alzheimer's Association International Conference, ALZ. Philadelphia, USA, and Online. July 28 – August 1, 2024.

The total testing cost for access to donanemab was $1,764 per patient (consisting of an MRI scan for 18% of patients ($441 per scan), 50% of patients undergoing amyloid testing through PET ($2,300 per scan) and 50% through CSF ($750 per test) and all patients undergoing an *APOE4* test ($160 per test)). The commentary noted that this cost increased to $2,130 per treated patient when considering patients who were tested for access to donanemab but were found ineligible.

Sensitivity analyses

Key sensitivity analyses on the testing parameters were conducted during the evaluation and were presented in Table 16. The model was sensitive to the proportion of patients undergoing the donanemab treat to clear strategy. This was expected given this directly relates to donanemab acquisition costs, a main contributor to the incremental costs between the two modelled arms.

Table 16 Key sensitivity analyses conducted during evaluation on the test parameters

Analyses	Inc. cost	Inc. QALYs	ICER	%
Base case	$REDACTED	0.42	$REDACTED [3]	—
% of amyloid positive patients during testing (base case: 85%)				
• 75% (TB-2 screening)	$REDACTED	0.42	$REDACTED [3]	REDACTED %
% of *APOE4* non-homozygotes during testing (base case: 64%)				
• 89%	$REDACTED	0.42	$REDACTED [3]	-REDACTED %
• 71%	$REDACTED	0.42	$REDACTED [3]	-REDACTED %
% of patients passing the pre-treatment MRI during testing (base case: 100%)				
• 89%	$REDACTED	0.42	$REDACTED [3]	REDACTED %
Sequential testing approach for donanemab (base case: not considered)				
• Included	$REDACTED	0.42	$REDACTED [3]	REDACTED %
% undertaking PET versus CSF AD biomarker tests (base case: 50% each)				
• 75% PET, 25% CSF	$REDACTED	0.42	$REDACTED [3]	REDACTED %
• 100% PET	$REDACTED	0.42	$REDACTED [3]	REDACTED %
• 100% CSF	$REDACTED	0.42	$REDACTED [2]	-REDACTED %
% of CSF tests that would be re-taken with PET (base case: 0%)				
• 100%	$REDACTED	0.42	$REDACTED [3]	REDACTED %
• 15% (% that would return a negative result)	$REDACTED	0.42	$REDACTED [3]	REDACTED %
Donanemab patients undergoing treat to clear strategy (base case: 40%)				
• 100%	$REDACTED	0.42	$REDACTED [1]	-REDACTED %
• 60%	$REDACTED	0.42	$REDACTED [2]	-REDACTED %
• 0%	$REDACTED	0.42	$REDACTED [4]	REDACTED %

Source: Constructed during the evaluation from the "3.3_Donanemab cost effectiveness model" attachment provided with the submission.
APOE = Apolipoprotein E gene; CSF = cerebrospinal fluid; ICER = incremental cost effectiveness ratio; Inc = incremental; MRI = magnetic resonance imaging; PET = positron emission tomography; QALY = quality-adjusted life year.
The redacted values correspond to the following ranges:
[1] $15,000 to <$25,000
[2] $25,000 to <$35,000
[3] $35,000 to <$45,000
[4] $45,000 to <$55,000

14. Financial/budgetary impacts

The key inputs for the financial estimates were summarised in Table 17.

Table 17 Key inputs for financial estimates

Parameter	Proportion	Rate	Basis / Source	Comment
MRI testing – eligibility	18%	1	82% of patients have already have a baseline MRI.	Remaining patients will require a baseline MRI prior to commencing treatment.
APOE ε4 genotyping – eligibility	100%	1	All MRI eligible patients.	This assumes that there is no need for additional testing due to test failure or indeterminant results.
Aβ-PET scan – eligibility	50%	1	All *APOE ε4* genotype eligible patients.	The submission assumes that 50% of patients will Aβ-PET scan. This is likely to be overestimated due to access constraints.
CT scan – eligibility	50%	1	All Aβ-PET scan patients.	The CT scan is required as part of the Aβ-PET scan. This is appropriate.
CSF AD biomarker testing – eligibility	50%	1	All *APOE ε4* genotype eligible patients.	The submission assumes that 50% of patients will Aβ-PET scan. This is likely to be underestimated due to overestimate of Aβ-PET scan utilisation.
Lumbar puncture – eligibility	50%	1	All CSF AD biomarker patients.	The lumbar puncture is required to obtain the CSF for testing. This is appropriate; however, the submission omitted several services associated with the lumbar puncture procedure.
CT scan – eligibility	50%	1	All CSF AD biomarker patients.	The CT scan is required as part of the lumbar puncture. This is appropriate.
Infusions	100%	12	1 infusion per dose of donanemab.	The submission assumes one dose per month, but donanemab is dosed Q4W which requires 13 doses annually. This underestimates the number of doses required.
MRI testing – monitoring	100%	4	Testing for ARIA prior to infusions 2,3,4 and 7.	This monitoring approach does not account for patients who will develop ARIA related symptoms at other time points and require an MRI scan to continue treatment. This underestimates the potential number of MRI scans required
Aβ-PET scan – monitoring	40%	1.38	Assessment of plaque in treat-to-clearance patients.	The submission assumes treat-to-clearance is 40% of the patient population. This may be overestimated because of the access constraints.
CT scan – monitoring	40%	1.38	All Aβ-PET scan patients.	The CT scan is required as part of the Aβ-PET scan. This is appropriate.

Source: Financial estimates workbook provided with the submission.

Table 18 Estimated use and financial implications in the submission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of *APOE4* genotyping						
Number of tests	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [7]	REDACTED [8]
Estimated extent of use of Aβ-PET scan (eligibility and monitoring)						
Number of tests	REDACTED [2]	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [7]
Estimated extent of use of CSF AD biomarker testing						
Number of tests	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]
Estimated extent of use of donanemab						
Number of scripts dispensed / infusions [a]	REDACTED [10]	REDACTED [11]	REDACTED [12]	REDACTED [13]	REDACTED [14]	REDACTED [15]
Estimated financial implications of the *APOE4* genotyping to the MBS						
Cost to the MBS	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [17]
Estimated financial implications of the Aβ-PET scan to the MBS						
Cost to the MBS	$ REDACTED [21]	$ REDACTED [22]	$ REDACTED [23]	$ REDACTED [25]	$ REDACTED [26]	$ REDACTED [26]
Estimated financial implications of the CSF AD biomarker testing to the MBS						
Cost to the MBS	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [17]	$ REDACTED [17]
Estimated financial implications for additional services to the MBS						
MRI scans – ARIA	$ REDACTED [19]	$ REDACTED [20]	$ REDACTED [21]	$ REDACTED [22]	$ REDACTED [24]	$ REDACTED [25]
CT scan with PET scan	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]
Lumbar puncture	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]
CT scan with LP	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]	$ REDACTED [16]
Attendance	$ REDACTED [18]	$ REDACTED [18]	$ REDACTED [19]	$ REDACTED [20]	$ REDACTED [21]	$ REDACTED [21]
Net financial implications						
Net cost to MBS	**$** REDACTED **[26]**	**$** REDACTED **[26]**	**$** REDACTED **[26]**	**$** REDACTED **[27]**	**$** REDACTED **[27]**	**$** REDACTED **[28]**
Net cost to MBS (evaluation estimates revised in Rejoinder[b])	**$** REDACTED **[26]**	**$** REDACTED **[26]**	**$** REDACTED **[26]**	**$** REDACTED **[27]**	**$** REDACTED **[27]**	**$** REDACTED **[28]**

[a] Assuming 12.1 scripts per course of treatment (treat to clearance) or 15.4 scripts per course of treatment (full duration treatment) as estimated by the submission.

[b] Evaluation response following submission's pre-ESC response.

Source: Table 4.22 – Table 4.29, pp317-320 of the submission.

The redacted values correspond to the following ranges per year:

[1] 10,000 to < 20,000
[2] 20,000 to < 30,000
[3] 30,000 to < 40,000
[4] 40,000 to < 50,000
[5] 50,000 to < 60,000
[6] 60,000 to < 70,000
[7] 70,000 to < 80,000
[8] 80,000 to < 90,000
[10] 200,000 to < 300,000
[11] 300,000 to < 400,000
[12] 400,000 to < 500,000

[13] 500,000 to < 600,000
[14] 600,000 to < 700,000
[15] 700,000 to < 800,000
[16] $0 to < $10 million
[17] $10 million to < $20 million
[18] $20 million to < $30 million
[19] $30 million to < $40 million
[20] $40 million to < $50 million
[21] $50 million to < $60 million
[22] $60 million to < $70 million
[23] $70 million to < $80 million
[24] $80 million to < $90 million
[25] $90 million to < $100 million
[26] $100 million to < $200 million
[27] $200 million to < $300 million
[28] $300 million to < $400 million

The submission used an epidemiological approach to calculate script and service volumes. The patient population was derived from the estimated system capacity to assess potential patients. The foundation of this derivation was the number of treating facilities, the number of clinics held and the number of patients a clinic can treat in a working week. A growth rate in the number of facilities and patient treatment days was then applied across the six years of the model. The submission assumed that private facilities were able to see twice as many patients each day as public facilities, based on the reported waiting times in each type of clinic.

The commentary considered that in a resource constrained system, it is reasonable to apply the constraint as a rate limiting step in system throughput. However, the results do not appear to be plausible for the number of facilities, or the treatment days provided by private facilities.

The commentary noted that the growth rate in the number of facilities is assumed to be the same as the growth rate in the number of neurologists and geriatricians. This is only valid if practitioners are sole practitioners in individual facilities or the "clinics" referred to in the submission are individual practitioners. The submission did not provide any evidence to support this assumption.

The commentary noted that the assumption that private facilities can see twice as many patients as public facilities coupled with an assumed 8% annual growth rate in daily patient consultations results in private facilities devoting more than 92% of their available time to assessing these patients by the model's sixth year. This would effectively leave no time for the on-going management of existing patients and the impossibility of treating any patient with an alternative condition.

The ADNeT 2023 Annual Report indicated that by 2060 approximately 850,000 people would be living with dementia, increasing from the 400,000 patients in 2023. Assuming that the growth of dementia is linear, by 2030 approximately 600,000 people will be living with dementia. If this figure is compared to the cumulative total of patients estimated to be initiated with donanemab shown in the submission (600,000 to <700,000), by the sixth year of the model (2030) more than all the prevalent dementia patients in Australia would be or would have been treated with donanemab.

The submission used the total number of new patients derived above, as if it were an incident population and then applied disease and eligibility criteria to determine the patients eligible for the three proposed MBS items – *APOE4* genotyping, Aβ-PET scan and CSF AD biomarker testing. The Aβ-PET scan is subsequently used to monitor patients to determine their eligibility to cease treatment. The details of the use and cost of these tests are shown below in Table 20.

Table 19 Estimated number of patients to be tested

		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Proportion of patients with MCI	37.0%	37.0%	37.0%	37.0%	37.0%	37.0%
B	Number of patients with MCI	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]	REDACTED [4]	REDACTED [5]
C	Proportion of patients with MCI due to AD	62.0%	62.0%	62.0%	62.0%	62.0%	62.0%
D	Number of patients with MCI due to AD	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [2]	REDACTED [3]
E	Proportion with MMSE ≥ 20	95.0%	95.0%	95.0%	95.0%	95.0%	95.0%
F	Number of patients with MMSE ≥ 20	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [2]	REDACTED [3]
G	Proportion of patients with dementia	63.0%	63.0%	63.0%	63.0%	63.0%	63.0%
H	Number of patients with dementia	REDACTED [4]	REDACTED [5]	REDACTED [5]	REDACTED [6]	REDACTED [7]	REDACTED [8]
I	Proportion of patients with dementia from AD	74.0%	74.0%	74.0%	74.0%	74.0%	74.0%
J	Number of patients with dementia from AD	REDACTED [3]	REDACTED [3]	REDACTED [4]	REDACTED [4]	REDACTED [5]	REDACTED [6]
K	Proportion with MMSE ≥ 20	75.0%	80.0%	85.0%	90.0%	95.0%	95.0%
L	Number of patients with MMSE ≥ 20	REDACTED [2]	REDACTED [3]	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]
M	Total number of patients with MMSE ≥ 20	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [8]	REDACTED [9]
N	Proportion of patients meeting MRI criteria	89.0%	89.0%	89.0%	89.0%	89.0%	89.0%
O	Number of patients meeting MRI criteria	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [7]	REDACTED [8]

Source: Worksheet *Appendix A* of the financial estimates model provided with the submission.

The redacted values correspond to the following ranges per year:

[1] 10,000 to < 20,000
[2] 20,000 to < 30,000
[3] 30,000 to < 40,000
[4] 40,000 to < 50,000
[5] 50,000 to < 60,000
[6] 60,000 to < 70,000
[7] 70,000 to < 80,000
[8] 80,000 to < 90,000
[9] 90,000 to < 100,000

Table 20 Submission's estimated use and financial implications – proposed tests

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of *APOE4* genotyping						
Number of patients tested [A]	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [7]	REDACTED [8]
Estimated financial implications of *APOE4* genotyping to the MBS						
Unit cost of the test [B]	$127.96	$127.96	$127.96	$127.96	$127.96	$127.96
Cost to the MBS [C=AxB]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [10]
Estimated extent of use of Aβ-PET scan – eligibility						
Number of patients tested [D]	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]
Estimated extent of use of Aβ-PET scan – monitoring						
Number of patients tested	REDACTED [1]	REDACTED [1]	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]
Number of tests required [E]	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [2]	REDACTED [3]
Estimated financial implications for Aβ-PET scan to the MBS						
Total number of tests [F=D+E]	REDACTED [2]	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [7]
Unit cost of the test [G]	$1,760.00	$1,760.00	$1,760.00	$1,760.00	$1,760.00	$1,760.00
Cost to the MBS [H=FxG]	$ REDACTED [12]	$ REDACTED [13]	$ REDACTED [14]	$ REDACTED [16]	$ REDACTED [17]	$ REDACTED [17]
Estimated extent of use of CSF AD biomarker testing – eligibility						
Number of patients tested [I]	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]
Estimated financial implications of CSF AD biomarker testing to the MBS						
Unit cost of the test [J]	$320.00	$320.00	$320.00	$320.00	$320.00	$320.00
Cost to the MBS [K=IxJ]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [10]	$ REDACTED [10]
Net financial implications						
Net cost to the MBS [C+H+K]	$ REDACTED [13]	$ REDACTED [14]	$ REDACTED [15]	$ REDACTED [17]	$ REDACTED [17]	$ REDACTED [17]

Source: Worksheet *7 Net changes – MBS* of the financial estimates model provided with the submission.

Cost is calculated at 80% of schedule fee.

B = $154 (proposed fee of *APOE* genotyping) + $5.95 (blood collection fee, MBS 73928), applied at 80% benefit.

G = $2,200 (proposed fee for Aβ-PET), applied at 80% benefit.

J = $400 (proposed fee for CSF AD biomarker testing), applied at 80% benefit.

The redacted values correspond to the following ranges per year:

[1] 10,000 to < 20,000
[2] 20,000 to < 30,000
[3] 30,000 to < 40,000
[4] 40,000 to < 50,000
[5] 50,000 to < 60,000
[6] 60,000 to < 70,000
[7] 70,000 to < 80,000
[8] 80,000 to < 90,000
[9] $0 to < $10 million
[10] $10 million to < $20 million
[11] $20 million to < $30 million
[12] $50 million to < $60 million
[13] $60 million to < $70 million
[14] $70 million to < $80 million
[15] $80 million to < $90 million
[16] $90 million to < $100 million
[17] $100 million to < $200 million

The proposed MBS items will require increased use of already listed MBS items. The proposed Aβ-PET scan will require a CT scan (MBS item 61505) with each test. The proposed CSF AD biomarker testing will require a lumbar puncture (MBS item 39000) and a CT scan (MBS item 61505) with each test. The lumbar puncture item also requires several anaesthesia items according to the characteristics of individual patients. The details of the use and cost of these items are shown in Table 23.

The following items were identified as required to support the lumbar puncture services during the evaluation.

Table 21 Additional anaesthesia items for lumbar puncture (compiled during evaluation)

Item	Rate	Reason
MBS 21945 - Initiation of management of anaesthesia	100%	All patients will require this service
MBS 17610 - Professional attendance by a medical practitioner (ANAESTHESIA)	100%	All patients will require this service
MBS 23010 - Anaesthesia, if the service time is not more than 15 minutes	50%	Assumption that half the patients will require a short anaesthesia service
MBS 23025 - Anaesthesia, if the service time is more than 15 minutes and less than 30 minutes	50%	Assumption that half the patients will require a long anaesthesia service
MBS 25000 - Anaesthesia, if the patient has severe systemic disease	25%	Assumption that a proportion of patients will have simple comorbidities
MBS 25005 - Anaesthesia, if the patient has severe systemic disease which is a constant threat to life	25%	Assumption that a proportion of patients will have complex comorbidities
MBS 25014 - Anaesthesia, if the patient is aged 75 years or more	50%	Assumption based on median age of patients reported in ADNet 2023 Report

Source: Developed during the evaluation based on Departmental advice.

Table 22 Estimated net cost of anaesthesia items for lumbar puncture to MBS (compiled during evaluation)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
MBS 21945 - Initiation of management of anaesthesia	REDACTED [3]	REDACTED [3]	REDACTED [4]	REDACTED [4]	REDACTED [5]	REDACTED [5]
Cost of MBS 21945	$90.20	$90.20	$90.20	$90.20	$90.20	$90.20
Cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]
MBS 17610 - Professional attendance by a medical practitioner (ANAESTHESIA)	REDACTED [3]	REDACTED [3]	REDACTED [4]	REDACTED [4]	REDACTED [5]	REDACTED [5]
Cost of MBS 17610	$39.80	$39.80	$39.80	$39.80	$39.80	$39.80
Cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]
MBS 23010 - Anaesthesia, not more than 15 minutes	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]	REDACTED [3]	REDACTED [3]
Cost of MBS 23010	$18.04	$18.04	$18.04	$18.04	$18.04	$18.04
Cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]
MBS 23025 - Anaesthesia, more than 15 and less than 30 minutes	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]	REDACTED [3]	REDACTED [3]
Cost of MBS 23025	$36.08	$36.08	$36.08	$36.08	$36.08	$36.08
Cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]
MBS 25000 - Anaesthesia, if the patient has severe systemic disease	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [2]	REDACTED [2]
Cost of MBS 25000	$18.04	$18.04	$18.04	$18.04	$18.04	$18.04
Cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]
MBS 25005 - Anaesthesia, if the patient has severe systemic disease which is a constant threat to life	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [2]	REDACTED [2]
Cost of MBS 25005	$36.08	$36.08	$36.08	$36.08	$36.08	$36.08
Cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]
MBS 25014 - Anaesthesia, if patient is aged 75 years +	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]	REDACTED [3]	REDACTED [3]
Cost of MBS 25014	$18.04	$18.04	$18.04	$18.04	$18.04	$18.04
Cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]
Total cost to the MBS	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]	$ REDACTED [6]

Source: Developed during the evaluation based on Departmental advice.
Fee for MBS 21945 is $112.75. Cost is calculated at 80% of schedule fee.
Fee for MBS 17610 is $49.75. Cost is calculated at 80% of schedule fee.
Fee for MBS 23010 is $22.55. Cost is calculated at 80% of schedule fee.
Fee for MBS 23025 is $45.10. Cost is calculated at 80% of schedule fee.
Fee for MBS 25000 is $22.55. Cost is calculated at 80% of schedule fee.
Fee for MBS 25005 is $45.10. Cost is calculated at 80% of schedule fee.
Fee for MBS 25014 is $22.55. Cost is calculated at 80% of schedule fee.
The redacted values correspond to the following ranges per year:
[1] 500 to < 5,000
[2] 5,000 to < 10,000
[3] 10,000 to < 20,000
[4] 20,000 to < 30,000
[5] 30,000 to < 40,000
[6] $0 to < $10 million

Table 23 Estimated use and financial implications – complementary items

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of CT scan with Aβ-PET scan – eligibility						
Number of patients tested	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]
Estimated extent of use of CT scan with Aβ-PET scan – monitoring						
Number of patients tested	REDACTED [1]	REDACTED [1]	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]
Number of tests required	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [2]	REDACTED [3]
Estimated financial implications for CT scan to the MBS						
Total number of tests	REDACTED [2]	REDACTED [3]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [7]
Unit cost of the test	$80.00	$80.00	$80.00	$80.00	$80.00	$80.00
Cost to the MBS	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]
Estimated extent of use of lumbar puncture with CSF AD biomarker testing						
Number of patients tested	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]
Estimated financial implications of lumbar puncture to the MBS						
Unit cost of the test	$68.60	$68.60	$68.60	$68.60	$68.60	$68.60
Cost to the MBS	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]
Estimated extent of use of CT scan with lumbar puncture						
Number of patients tested	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [3]	REDACTED [3]
Estimated financial implications of CT scan to the MBS						
Unit cost of the test	$211.00	$211.00	$211.00	$211.00	$211.00	$211.00
Cost to the MBS	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]
Estimated financial implications of anaesthesia with lumbar puncture to the MBS						
Cost to the MBS	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]	$ REDACTED [8]
Net financial implications						
Net cost to the MBS	$ REDACTED [8]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [9]	$ REDACTED [10]

Source: Worksheet 7 Net changes – MBS of the financial estimates model provided with the submission.
Source: Anaesthesia items were developed during the evaluation based on Departmental advice.
Cost is calculated at 80% of schedule fee.
The redacted values correspond to the following ranges per year:
[1] 10,000 to < 20,000
[2] 20,000 to < 30,000
[3] 30,000 to < 40,000
[4] 40,000 to < 50,000
[5] 50,000 to < 60,000
[6] 60,000 to < 70,000
[7] 70,000 to < 80,000
[8] $0 to < $10 million
[9] $10 million to < $20 million
[10] $20 million to < $30 million

Eligibility for donanemab requires patients to have no evidence of superficial siderosis or > 2 cerebral microhaemorrhages. This is confirmed through an MRI scan (MBS item 63004). The

commentary considered that the MBS item descriptor for the existing MBS item 63004 will need to be broadened to allow this use or an additional MBS item created.

Once patients commence treatment with donanemab, they require monitoring to detect the development of amyloid-related imaging abnormalities (ARIA) that will require either dose adjustments or cessation. This monitoring is confirmed through an MRI scan (MBS item 63004).

The details of the use and cost of these items are shown below in Table 24.

Table 24 Estimated use and financial implications – MRI items

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of MRI scan – eligibility						
Number of patients tested	REDACTED [1]	REDACTED [1]	REDACTED [2]	REDACTED [2]	REDACTED [2]	REDACTED [2]
Estimated extent of use of MRI scan – monitoring						
Number of patients tested	REDACTED [3]	REDACTED [4]	REDACTED [4]	REDACTED [5]	REDACTED [6]	REDACTED [7]
Number of tests required	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [9]	REDACTED [9]
Revised number of tests	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [9]	REDACTED [9]
Estimated financial implications for MRI scan to the MBS						
Total number of tests	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [9]	REDACTED [9]
Revised number of tests	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [8]	REDACTED [9]	REDACTED [9]
Unit cost of the test	$353.16	$353.16	$353.16	$353.16	$353.16	$353.16
Net cost to the MBS	$ REDACTED [10]	$ REDACTED [11]	$ REDACTED [12]	$ REDACTED [13]	$ REDACTED [15]	$ REDACTED [16]
Revised cost to the MBS	*$* REDACTED [10]	*$* REDACTED [11]	*$* REDACTED [12]	*$* REDACTED [13]	*$* REDACTED [14]	*$* REDACTED [16]

Source: Worksheet *7 Net changes – MBS* of the financial estimates model provided with the submission.
Cost is calculated at 80% of schedule fee.
Note: Italics show corrections applied during the evaluation. The number of tested patients was overestimated by using patient years of treatment rather than patients in the calculation.
The redacted values correspond to the following ranges per year:
[1] 5,000 to < 10,000
[2] 10,000 to < 20,000
[3] 20,000 to < 30,000
[4] 30,000 to < 40,000
[5] 40,000 to < 50,000
[6] 50,000 to < 60,000
[7] 60,000 to < 70,000
[8] 100,000 to < 200,000
[9] 200,000 to < 300,000
[10] $30 million to < $40 million
[11] $40 million to < $50 million
[12] $50 million to < $60 million
[13] $60 million to < $70 million
[14] $70 million to < $80 million
[15] $80 million to < $90 million
[16] $90 million to < $100 million

The total financial impact on the MBS of the listing of donanemab on the PBS is shown below in Table 25. This total does not include the MBS item (MBS item 116) associated with the administration of donanemab.

Table 25 Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Proposed MBS items	$ REDACTED [7]	$ REDACTED [8]	$ REDACTED [9]	$ REDACTED [11]	$ REDACTED [11]	$ REDACTED [11]
Increased MBS items	$ REDACTED [1]	$ REDACTED [2]	$ REDACTED [2]	$ REDACTED [2]	$ REDACTED [2]	$ REDACTED [3]
Increased MRI scans	$ REDACTED [4]	$ REDACTED [5]	$ REDACTED [6]	$ REDACTED [7]	$ REDACTED [9]	$ REDACTED [10]
Revised MRI scans	*$* REDACTED [4]	*$* REDACTED [5]	*$* REDACTED [6]	*$* REDACTED [7]	*$* REDACTED [8]	*$* REDACTED [10]
Net cost to the MBS	$ REDACTED [11]	$ REDACTED [11]	$ REDACTED [11]	$ REDACTED [11]	$ REDACTED [12]	$ REDACTED [12]
Revised cost to the MBS	$ REDACTED [11]	$ REDACTED [11]	$ REDACTED [11]	$ REDACTED [11]	$ REDACTED [12]	$ REDACTED [12]

Source: Worksheet *7 Net changes – MBS* of the financial estimates model provided with the submission.
Cost is calculated at 80% of schedule fee.
Note: *Italics* show corrections applied during the evaluation.
The redacted values correspond to the following ranges per year:
[1] $0 to < $10 million
[2] $10 million to < $20 million
[3] $20 million to < $30 million
[4] $30 million to < $40 million
[5] $40 million to < $50 million
[6] $50 million to < $60 million
[7] $60 million to < $70 million
[8] $70 million to < $80 million
[9] $80 million to < $90 million
[10] $90 million to < $100 million
[11] $100 million to < $200 million
[12] $200 million to < $300 million

15. Other significant factors

Health system capacity

The submission estimated that of the 30,000 to <40,000 (Year 1) patients with MCI due to AD or mild AD, 30,000 to <40,000 (Year 1) individuals would undergo Aβ pathology testing, split 50/50 between Aβ-PET and CSF AD biomarker testing.

Two additional Aβ-PET scans would also be required to determine if there has been clearance of the amyloid plaques while on treatment.

Each person treated would also require multiple additional MRI brain scans to monitor for the appearance of amyloid-related imaging abnormalities (ARIAs), noting the safety concerns associated with donanemab treatment.

The commentary considered that this level of resource use would place significant pressure on the current capacity of the health care system and it is uncertain how this would be implemented in the short term. Either many eligible patients will miss out on testing, safety monitoring and/or treatment, or the services will be performed with the effect of increasing wait times for diagnostic imaging services, meaning delays in access to PET and MRI services across the community. The alternative would be increasing capital outlays on PET and MRI equipment.

Additional resources would also be required for infusion of the drug, both in the public hospital system and through the use of MBS items for consultations and administering the drug.

The TGA-approved PI for donanemab states that "KISUNLA should be administered in specialised centres under the supervision of a multidisciplinary team trained in detection, monitoring and management of ARIA and experienced in detecting and managing infusion related reactions. These centres will likely need to be established.

A national, cross-sectional survey was conducted from 7 September 2023 to 7 February 2024, and the results were published in the *Internal Medicine Journal* in 2025 to gauge Australia's capacity and readiness for the rollout of Aβ-targeting therapies for AD. Specialist clinicians who responded to the survey raised concerns about the IV administration of anti-Aβ drugs, mostly centred around 'staffing needs', 'location', 'resources/infrastructure needs' as well as 'capacity'.

Accessibility issues

The commentary noted that there is a significant financial impact for rural and remote patients. To receive the rebate for a Medicare eligible MRI or PET scan, a patient requires a specialist referral, which first requires a visit to a GP. Both visits are likely to incur out-of-pocket costs for the patient and are in addition to any travel, accommodation and the out-of-pocket costs associated with receiving the scan. Multiple scans will result in a significant financial impost.

The commentary considered that access to Aβ-PET scanning in Australia is also likely to be problematic due to the production of amyloid radiopharmaceuticals being limited to a few sites, such as Cyclotek's manufacturing facilities in Victoria, New South Wales, and Queensland, and some hospital nuclear medicine departments with onsite cyclotrons.

Additionally, the radiopharmaceuticals have a short half-life (~110 minutes), posing a challenge for timely delivery. This constraint is exacerbated by the vast geographic distances in Australia

Clinical specialists have indicated that use of lumbar puncture is not widespread in Australia and may not be as acceptable to patients as non-invasive PET scanning.

Currently the CSF test is only available from two pathology testing laboratories who have received National Association of Testing Authorities (NATA) accreditation for the use of the Elecsys® CSF assays.

Timely processing of patient samples will require increased capacity at these two pathology laboratories as well as additional laboratories being accredited to offer this service. This would also require the establishment of a Quality Assurance Program to ensure the reliability and reproducibility of results between diagnostic laboratories.

According to the Royal College of Pathologists of Australasia (RCPA) website, *APOE* genotyping is available through five member laboratories in Australia.

Timely processing of all patient samples will require increased capacity with additional laboratories being accredited to offer *APOE* genotyping. A Quality Assurance Program would also need to be established.

AD biomarker testing using plasma instead of CSF

The submission noted that emerging blood-based biomarkers (BBB) have the potential to be accurate, cost-effective, and easily accessible for widespread clinical use, and could become important tools for AD evaluation in the future.

In Australia, BBB tests are not currently subsidised on the MBS, however, the PrecivityAD2 test is offered for a non-rebated fee of $1,495 by the private pathology provider Laverty Pathology. Laverty Pathology currently send blood samples to the C2N diagnostics laboratory in the United States, and it takes approximately 4 weeks to receive the test results.

The submission identified four studies that compared the diagnostic accuracy of BBB tests with Aβ-PET. During evaluation, a rapid non-systematic literature search identified an additional six studies comparing BBB with Aβ-PET.

These studies found that the measurement of the Aβ42/Aβ40 ratio may be less robust when using plasma samples compared with CSF samples for testing. They also concluded that plasma Aβ42/Aβ40 would pose significant challenges, with misclassification risks if implemented for routine clinical use, partly because variation between tests greatly affected the use of plasma Aβ42/40 in discriminating Aβ status.

In contrast, p-tau217 had comparable performance in both plasma and CSF and has potential for use in the diagnosis and screening for AD. When measuring plasma p-tau217 levels or the ratio of phosphorylated to non-phosphorylated tau217 (p-tau217/np-tau217), the median ROC-AUC varies from 0.918 to 0.93. This is very comparable to the median ROC-AUC values for CSF ratios of Aβ42/Aβ40, p-tau181/Aβ42 and t-tau/Aβ42, which vary from 0.894 to 0.953. Thus, the commentary considered that the BBB p-tau217 is a robust candidate for predicting Aβ pathology via a blood test, potentially reducing the need for either Aβ-PET or lumbar puncture for CSF AD biomarker testing in the near future.

The Australian Dementia Network is already running a trial of the pTau-217 blood biomarker test in primary care settings in Adelaide, Newcastle and north-eastern Melbourne[10]. They have also asked for Federal Government funding of an Australian testing centre at the Florey NATA-accredited laboratory to "make the test widely available to Australians in the short term and facilitate the processes for TGA approval and Medicare coverage."

On 16 May 2025, the FDA, approved the use of the blood test, Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio, "for the early detection of amyloid plaques associated with Alzheimer disease in adult patients, aged 55 years and older, exhibiting signs and symptoms of the disease."

[10] Auld and Hoffman. 2025. Alzheimer's blood test coming soon to Australia URL: https://www.healthed.com.au/clinical_articles/alzheimers-blood-test-coming-soon-to-australia/ published 28 March 2025, assessed 19 May 2025

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

- Issue of discordance between the results from Aβ PET scans and CSF AD biomarker testing to detect Aβ pathology: The ESCs considered that an overall assessment of the comparative safety and clinical effectiveness of test and treatment with donanemab (+SOC) versus no testing and treatment with SOC should incorporate consideration of the discordance between results from Aβ PET scans and CSF AD biomarker testing (i.e., false positives and false negatives). The ESCs noted that the pivotal trial (TB-2) used Aβ PET scan results to detect Aβ pathology and that CSF AD biomarker testing was not used in this trial. The ESCs noted that the submission did not assess the impact (benefits, harms) of discordant results from Aβ PET and CSF AD biomarker testing on subsequent unnecessary treatment from false positives or inappropriate omission of treatment from false negatives.

Economic issues

- The ESCs considered the submission model's exclusion of consideration of false positive/false negative test results from Aβ PET and CSF AD biomarker testing rendered the modelled comparative safety and clinical effectiveness incomplete and uncertain, with unclear impact on downstream resource use and increased uncertainty in the cost-effectiveness results. The ESCs noted that all patients entered the model at the point of treatment rather than at the point of testing. As such, the submission's model did not include consideration of the impact of false positives (unnecessary donanemab treatment, incurring greater costs with no benefit but with potential harms from adverse events) and monitoring) or false negatives (missing out on donanemab treatment) in the assessment of overall cost-effectiveness.

Financial issues

- The ESCs noted the substantial net cost to the MBS with the proposed listings, totalling an estimated >$1 billion (Table MSAC 19; 8% of the >$1 billion net increase in health budget) in the first 6 years of listing).
- The ESCs considered the submission's use of a 'bottom-up' approach, based on estimated system capacity for diagnosing and assessing patients for treatment, to estimate eligible patient numbers for tests (and subsequent treatment) inappropriate. The ESCs considered that utilisation should estimate the entire eligible population with varying uptake rates applied subsequently to account for system capacity, to estimate the total financial impact to the health system. In addition, the ESCs considered that a full budget impact assessment should include downstream impact considerations of varying the assumed split between treat-to-clear versus treat for the full 18 months (e.g., scenario considerations where 100% of eligible patients are treated to clear with full access to PET scanning, or 100% of the eligible patients are treated for a full 18 months but with no PET access).
- The ESCs considered that the financial estimates are subject to further uncertainties as the following parameters were not well supported: the prevalence of *APOE4* homozygosity in Australia (which will affect the number of patients tested for Aβ pathology), and the differential uptake rates of Aβ PET and CSF AD biomarker testing to determine Aβ pathology (impacting on costs as the proposed MBS fees for the two test options are different as well as use of other associated services). The ESCs noted that access to PET machines may also have an impact on the proportion of patients treated to clear or treated for the full 18 months, although clinicians are likely to minimise donanemab treatment given its adverse events profile.

Other relevant factors

- There will be accessibility issues for both PET and CSF tests, as well as for *APOE* genotyping. These are discussed further in the 'Main issues for MSAC and PBAC consideration' box.

Patients outside major capital cities may be more likely to have continued treatment for 18 months without PET monitoring as this testing may not be available locally.

- Using plasma instead of CSF to measure AD biomarkers, especially plasma p-tau217, may be feasible in the near future, potentially reducing the need for either Aβ-PET or lumbar puncture for CSF AD biomarker testing. The ESCs, however, considered that while a blood test to determine Aβ pathology may resolve some of the issues with using PET scanning or CSF testing, other health system capacity challenges remain. The department noted that the FDA (Food and Drug Administration) have approved the blood based biomarker based on its correlation with the CSF AD biomarker testing only.

ESCs discussion

The Joint MSAC Evaluation Subcommittee/PBAC Economics Sub Committee (hereafter referred to as the ESCs) noted that the integrated codependent application sought:

- Medicare Benefits Schedule (MBS) funding for (1) 2 testing options to detect amyloid-beta (Aβ) pathology, using either Aβ Positron Emission Tomography (Aβ-PET) of the brain or Cerebrospinal Fluid (CSF) AD biomarker testing; and (2) apolipoprotein E (*APOE*) genotyping prior to Aβ pathology testing, in patients with a clinical diagnosis of mild cognitive impairment (MCI) due to Alzheimer Disease (AD) or mild AD, to determine eligibility for PBS-subsidised treatment with donanemab.
- Pharmaceutical Benefits Scheme (PBS) Section 100 (Highly Specialised Drugs Program) Authority Required (Telephone) listing of donanemab for the treatment of patients with early symptomatic AD, defined in the submission as MCI due to AD or mild AD.

The ESCs noted that Aβ PET and CSF AD biomarker testing to detect Aβ pathology to access lecanemab was scheduled to be considered by ESCs in June 2024 (MSAC application 1738).

Clinical

The ESCs noted that the AD continuum is a progression through various stages, broadly categorised as preclinical AD (presence of Alzheimer-related brain changes but no noticeable cognitive decline or outward symptoms), MCI due to AD (noticeable decline in cognitive abilities), and dementia due to AD (categorised as mild, moderate, severe). The ESCs considered that there is considerable uncertainty in the diagnosis of patients with MCI due to AD and mild AD due to the absence of reliable diagnostic tools and subjectivity in making the clinical assessment.

APOE genotyping

The ESCs considered the proposed *APOE* genotyping prior to testing for Aβ pathology to be appropriate. The ESCs noted that *APOE4* status is a genetic risk factor for developing AD.

The ESCs considered that *APOE4* homozygous and heterozygous prevalence rates in Australia are unclear. The ESCs noted that the submission estimated the prevalence of *APOE4* homozygosity in Australia to be approximately 6% but used a higher prevalence rate of 10.9% to estimate the number of patients who would be ineligible for donanemab treatment. The ESCs noted that international studies have reported *APOE4* homozygous rates as 2% of total population and 15% in patients with AD.[11] The ESCs requested further information from the

[11] Gharbi-Meliani, A., Dugravot, A., Sabia, S., Regy, M., Fayosse, A., Schnitzler, A., Kivimäki, M., Singh-Manoux, A., & Dumurgier, J. (2021). The association of APOE ε4 with cognitive function over the adult life course and incidence of dementia: 20 years follow-up of the Whitehall II study. *Alzheimer's Research & Therapy*, *13*(1), Article 5. https://doi.org/10.1186/s13195-020-00740-0.

applicant regarding *APOE4* genotype frequencies (homozygous, heterozygous and non-carriers) in the Australian population.

The ESCs noted that donanemab is TGA-registered for the treatment of patients with MCI due to AD and Mild Alzheimer dementia (Early Symptomatic Alzheimer disease) who are *APOE4* heterozygotes or non-carriers and that testing for *APOE4* status is required prior to initiation of treatment to inform the risk of developing amyloid-related imaging abnormalities (ARIA) in the brain. Patients who are *APOE4* homozygous are contraindicated to treatment with donanemab due to the higher risk of amyloid-related imaging abnormalities (ARIAs), compared to *APOE4* heterozygotes. The ESCs considered ARIAs to be true pathologies (cerebral oedema and haemorrhage) as opposed to imaging artefacts as might be implied by their name.

The ESCs considered prevalence of *APOE4* heterozygosity and homozygosity may not be applicable to the Australian population as the key trials were in predominantly people of European ancestry and *APOE4* status is associated with ancestry. In particular, the ESCs considered rates of *APOE4* heterozygosity may be substantially different for Aboriginal and Torres Strait Island populations.[12,13,14]

The ESCs noted that the submission proposed that patients must undergo blood-based polymerase chain reaction (PCR) *APOE4* genotyping to determine eligibility for Aβ pathology testing and subsequent donanemab treatment but did not specify the type of PCR-based genotyping method that would be used in Australian diagnostic laboratories.

The ESCs noted that the commentary reported that real-time-PCR-based techniques, including high resolution melt, TaqMan probe and Fluorescent Resonance Energy Transfer (FRET) methods are currently the most relevant methods for diagnostic genotyping. The ESCs noted the commentary's rapid non-systematic literature review concluded that the various PCR-based genotyping methods are highly concordant and highly accurate, compared to Sanger sequencing (94-100%), the gold reference standard for determining the *APOE* genotype and has a PCR component.

The ESCs noted that there are several *APOE* PCR-based genotyping tests available commercially, with unclear TGA-registration status. See paragraph Implementation below for further information.

Aβ PET brain scan

The ESCs considered a key issue with Aβ PET scan of the brain is its reliability in detecting clinical AD.

The ESCs noted the commentary's review concluded that Aβ PET using ^{18}F-flutemetamol (FMM), ^{18}F-florbetaben (FBB) or ^{18}F-florbetapir (FBP) showed relatively high sensitivity and specificity (pooled estimate, 93% and 91%, respectively) and provides a reliable test for determining Aβ pathology.

However, the ESCs considered that the correlation between Aβ pathology and AD to be unclear, noting that Aβ may also be found in the brains of individuals without symptoms of MCI or AD. Indeed, a proportion (20%-30%) of cognitively normal individuals or individuals with other (non-

[12] Seto M et al. RNASE6 is a novel modifier of APOE-ε4 effects on cognition. *Neurobiol Aging*. 2022;118:66-76

[13] Lavrencic LM et al. Dementia Incidence, *APOE* Genotype, and Risk Factors for Cognitive Decline in Aboriginal Australians: A Longitudinal Cohort Study. *Neurology*. 2022;98(11):e1124-e1136

[14] Nguyen HXT et al. Risk, protective, and biomarkers of dementia in Indigenous peoples: A systematic review. *Alzheimers Dement*. 2024;20(1):563-592.

AD) dementia test positive on amyloid PET and this proportion increases to 50% in older individuals who are *APOE4* positive. Additionally, the ESCs noted that the positive predictive value of Aβ PET to detect AD is highest in younger patients (late 40s to early 50s) with a high pretest probability of AD, based on clinical evaluation. Both positive and negative predictive values of Aβ PET are less reliable in older patients, particularly in those who are *APOE4* positive.[15]

The ESCs noted that the proposed tests to detect Aβ pathology were either the Aβ PET scan of the brain or cerebrospinal fluid (CSF) AD biomarker test. The ESCs further noted that the pivotal TRAILBLAZER-ALZ 2 (TB-2) trial used the Aβ PET scan exclusively to detect Aβ pathology and did not include CSF AD biomarker testing. The ESCs therefore considered the implications of donanemab treatment in patients who test 'negative' on Aβ PET scans but 'positive' on CSF AD biomarker testing unknown, as acknowledged in the Pre-Sub-Committee Response (PSCR). The ESCs considered that it was important to incorporate considerations of false positive and false negative results of Aβ PET in the overall assessment of the comparative safety and clinical effectiveness of test and donanemab (+ SOC) treatment versus no testing and SOC treatment.

The ESCs noted several implementation issues with Aβ PET. See Implementation paragraph below for further information.

CSF AD biomarker test

The ESCs considered a key issue with the proposed use of the CSF AD biomarker test as an alternative to Aβ PET brain scan to detect Aβ pathology is the discordance in the results of the two test options.

The ESCs noted the commentary's systematic review on the diagnostic test accuracy of CSF AD biomarker testing in AD reported a pooled sensitivity and specificity of 89.4% and 70.5%, respectively, when compared to neuropathology at autopsy. The ESCs noted that sensitivity and specificity of CSF AD biomarker testing are lower than for Aβ PET. Based on these results, the ESCs agreed with the commentary that when compared with Aβ PET brain scanning, CSF AD biomarker testing is likely to result in more patients with false negative (who would then be inappropriately omitted of donanemab treatment) and false positive (who would receive unnecessary donanemab treatment) results.

The ESCs noted the commentary's review of studies that directly compared the concordance of CSF AD biomarker testing and Aβ PET (FBB or FBP): 2-19% of Aβ-PET positive tests would be CSF Aβ42 negative and 6-28% of Aβ-PET negative tests would be CSF Aβ42 positive (Table MSAC 12). The PSCR acknowledged the commentary's concordance assessment but also stated that if consideration was limited to pTau/Aβ42 and tTau/Aβ42 ratios, then 7–19% of Aβ-PET positive tests would be CSF Aβ42 negative, and only 6–13% of Aβ-PET negative tests would be CSF Aβ42 positive, as per the commentary's concordance review. The ESCs noted the PSCR reported that pTau/Aβ42 and tTau/Aβ42 ratios are the results provided by Elecsys® AD CSF portfolio (Roche Diagnostics), the only TGA-registered CSF immunoassay currently available. Nevertheless, the ESCs considered the degree of discordance between Aβ-PET and CSF AD biomarker testing remained uncertain and would have flow-on effects to the assessment of overall treatment benefits and harms and cost-effectiveness.

15 Bergeron et al. Evidence-based Interpretation of Amyloid-β PET results. *Alzheimer Dis Assoc Disord* 32(1); 2018: 28-34"

Clinical claim

The ESCs noted the submission's claim that in patients with early symptomatic AD, amyloid testing (Aβ PET or CSF AD protein biomarker testing) followed by treatment with donanemab + SOC in patients with evidence of Aβ pathology was superior to no amyloid testing and treatment with SOC in terms of effectiveness and has an inferior but manageable safety profile.

The ESCs noted that for the proposed testing modalities, the evidence base presented was limited to one sponsor-funded group of associated trials. The ESCs considered that while the pivotal randomised placebo-controlled trial (TB-2) was of reasonable quality, its relevance and applicability to the Australian target population was limited, as TB-2 included only patients who met Aβ PET scan eligibility criteria and CSF AD biomarker testing was not used. The ESCs considered that while TB-2 might be adequate to assess the effect of donanemab on amyloid clearance, this is a surrogate outcome and donanemab's effect on clinical outcomes is less certain.

Based on the data the submission presented, the ESCs considered that the estimated clinical differences were modest. The ESCs considered that it was highly uncertain if the degree of slowing in clinical progression was clinically meaningful and if it would produce a noticeable benefit to patients and caregivers. In addition, the ESCs considered that the effect of amyloid clearance on the clinical effects and progression of AD remained uncertain.

The ESCs noted the role of *APOE4* genotyping and MRI monitoring for ARIAs is to address the safety issues associated with donanemab treatment. Based on the data the submission presented, the ESCs considered the claim of inferior comparative safety supported.

- The ESCs noted that the rationale of testing for *APOE4* status prior to the initiation of donanemab treatment was to identify *APOE4* homozygous patients such that they are excluded from donanemab treatment, due to their higher risk of ARIA events. The ESCs noted that this testing rationale is different from the general case of testing to identify patients who may benefit from therapy. The ESCs noted that in the TB-2 trial, *APOE4* homozygotes were at greater risk of ARIA, compared to *APOE4* heterozygotes or non-carriers (serious events of ARIA 3%, 2% and 1%, respectively). The ESCs noted that ARIA events are potential serious or fatal cerebral complications, , and are not imaging artefacts of little clinical significance.
- The ESCs noted the adverse events from Aβ PET scanning (e.g., headache, injection site pain, potential harms from radiation exposure).
- The ESCs noted the adverse events associated with CSF AD biomarker testing, including those related to lumbar puncture, CT guidance, and anaesthesia if required. The submission considered lumbar puncture to be a safe procedure with <1% of serious reported events needing specialist treatment. However, the ESCs noted that the incidence of post-dural puncture headache (PDPH), which can occur following lumbar puncture can range between 2-75%, depending on factors such as proceduralist experience and patient age[16] and that a significant proportion of patients with PDPH may require an epidural blood patch, performed in hospital by an anaesthetist.

Consultation input

The ESCs noted and welcomed consultation feedback received for the testing component of the current application as of the date of the ESCs consideration. This included input from one

[16] Hatfield MK, Handrich SJ, Willis JA, Beres RA, Zaleski GX. Blood patch rates after lumbar puncture with Whitacre versus Quincke 22- and 20-gauge spinal needles. *AJR Am J Roentgenol*. 2008 Jun;190(6):1686-9. doi: 10.2214/AJR.07.3351. PMID: 18492925.

organisation (Dementia Australia) and four individuals. The ESCs noted from the input the significant and multifaceted impacts of AD on individuals and their families, and the view that donanemab, while not a cure, may slow progression of the disease and aid future planning. The input also highlighted the importance of early/timely diagnosis of the disease to allow for the appropriate and effective use of donanemab and emphasised the need for equitable access. The ESCs noted that there may be considerable costs to patients in accessing the proposed interventions (e.g. travel costs) and considered that targeted investments may be required to ensure that already existing inequalities in access to care are not further exacerbated. The ESCs considered that access to the proposed tests and the drug should be equitable, and patient-centred.

Economic

The ESCs noted that the submission presented a modelled economic evaluation (cost-utility analysis, CUA) based on the treatment effect observed in the TB-2 trial which compared donanemab treatment to SOC in patients with early AD with a positive Aβ biomarker test and who were not *APOE4* homozygous.

The ESCs noted that all patients entered the model at the point of treatment rather than at the point of testing. The ESCs noted that the commentary considered it reasonable as the model included the testing costs for all patients considered for donanemab. The ESCs however, disagreed. The ESCs considered that the economic evaluation should consider the whole population, both tested and treated populations, especially in the context of two alternative tests for Aβ pathology which may have discordant results to determine access to a drug and the pivotal trial used only one of the tests. The ESCs noted that the tested population will be larger than the treated population, due to a proportion of patients testing negative on the test to determine the presence of Aβ pathology and therefore becoming ineligible for treatment. The ESCs considered the submission model's exclusion of false positive/false negative test results rendered the modelled comparative safety and clinical effectiveness incomplete and uncertain, increasing the uncertainty in the cost-effectiveness results.

The ESCs noted that the submission's model assumed a 50/50 split of patients undergoing Aβ PET brain scan or CSF AD biomarker testing to detect Aβ pathology to access donanemab treatment. The ESCs considered the assumption of 50/50 split was not well supported but noted that the incremental cost-effectiveness ratio (ICER) increased only slightly (REDACTED % increase) from $35,000 to <$45,000 (base case) to $35,000 to <$45,000 per quality-adjusted life year (QALY) gained, assuming 100% used Aβ PET.

The ESCs noted the submission's economic model was sensitive to the proportions of patients undergoing donanemab treat-to-clear/treat to 18 months strategies, with the ICER increasing (by REDACTED %) to $45,000 to <$55,000/QALY gained when assuming 100% of donanemab patients receiving full 18 months of treatment (base case 60%).

Overall, the ESCs considered the submission's economic model overly optimistic (e.g., unknown duration of treatment effect, modelled treatment effect at 15 years based on a modest 1.38-month delay in progression after 76 weeks of treatment).

Financial

The ESCs noted the substantial net cost to the MBS with the proposed listings (commentary's revised estimates in Rejoinder): $100 million to <$200 million in Year 1, rising to $300 million to <$400 million in Year 6, totalling >$1 billion in the first 6 years of listing, representing 8% of the total net increase in health budget (Table MSAC 19).

The ESCs noted that the submission used a 'bottom-up' approach, based on estimated service capacity for diagnosing and assessing patients for treatment, to estimate eligible patient numbers for tests (and treatment).

- The ESCs noted that the submission reported it challenging to accurately quantify the number of patients likely to undergo tests (and therefore initiate donanemab) due to the lack of robust prevalence and incidence data for dementia and MCI in Australia.
- The ESCs noted that rather than using a standard epidemiological approach to estimate patient numbers for tests, the submission based its estimates on the existing number of specialist memory and cognition assessment services (estimated N=163) in Australia, assumed an annual growth rate (6.4%) consistent with the historical growth in registered neurologists and geriatricians across Australia, and applied a range of assumptions (e.g., 3.1/3.7 new patients seen per public/private clinic day, 1.45/2.90 public/private clinic days per week with arbitrary 8% constant growth p.a., 48 working weeks/year).

The ESCs considered the submission's use of a system capacity approach to estimate eligible patient numbers inappropriate. The ESCs considered that the financial assessment should capture the whole eligible population to estimate the total financial impact to the MBS assuming no system constraints, with varying uptake rates applied subsequently to account for system capacity.

The ESCs noted a number of the submission's assumptions appeared arbitrary, e.g., private assessment services offer double the number of clinic days per week than in public services, 8% growth p.a. in the number of clinic days/week, 48 working weeks/year.

The ESCs noted a significant potential use of general anaesthesia with PET and MRI scans, especially in a patient population likely to be confused and/or anxious and/or difficult to communicate with. However, this had not been costed and included in the financial estimates.

The ESCs noted that the commentary considered the treat-to-clear population, assumed to be 40% of eligible patients in the submission, was likely overestimated as some patients might not be able to access Aβ PET scanning to determine amyloid clearance. However, the ESCs considered that clinicians would likely want to minimise time on treatment as donanemab is an IV therapy with a risk of ARIA events.

The ESCs agreed with the commentary that there is potential for leakage of both Aβ PET scanning and CSF AD biomarker testing use beyond the intended purpose of determining access to donanemab treatment (e.g., to initiate treatment with other medications like cholinesterase inhibitors or memantine). In addition, the ESCs considered that in clinical practice, some patients might seek to receive both Aβ PET and CSF AD biomarker testing (i.e., one after the other if the first result is negative, rather than one or the other) in order to access donanemab if PBS-listed. The ESCs noted that the Department intends to monitor the items' usage, out-of-pocket costs and co-claiming of these items, consult with stakeholders regarding service access, and seek advice from the MSAC Executive for item descriptor amendment if required.

Overall, the ESCs reiterated that the financial assessment should capture the entire eligible population to estimate the total financial impact to the MBS assuming no system constraints, with varying uptake rates applied subsequently to account for system capacity. The ESCs considered that a full budget impact assessment should also include downstream impact considerations of varying the assumed split between treat-to-clear versus treat for the full 18 months (e.g., scenario considerations where 100% of eligible patients are treated to clear with full access to PET scanning, or 100% of the eligible patients are treated for a full 18 months but with no PET access).

The ESCs noted that the PBAC's Drug Utilisation Sub-Committee (DUSC) considered donanemab in June 2025.

Proposed MBS listings

The ESCs noted that the submission requested a new MBS item for each of the following new tests: *APOE* genetic testing (Table MSAC 2), Aβ-PET scan of the brain (Table MSAC 4), CSF AD biomarker testing (Table MSAC 5) and Aβ-PET monitoring to assess amyloid clearance (Table MSAC 6).

The ESCs agreed with the department's proposed removal of reference to a specific drug in the item descriptors, for future-proofing purpose.

For the proposed service for *APOE* genetic testing, the ESCs considered that it is important to restrict usage to once per lifetime (Table MSAC 3).

For the proposed service for CSF AD biomarker testing, the ESCs noted that the proposed item (Table MSAC 5) only includes pathology testing and collection requires separate costing. The ESCs considered that the number of patients who may require anaesthesia or sedation for a lumbar puncture was uncertain and that elderly patients are likely to benefit from CT guidance.

For the use of Aβ PET to monitor amyloid clearance at 24 and 52 weeks of treatment, the ESCs considered that it is appropriate to specify that the proposed item is applicable up to a total of 2 services (Table MSAC 6). The ESCs noted that patients who do not have access to PET scans for monitoring purposes (e.g., in remote/regional areas) may receive unnecessary donanemab treatment (i.e., treatment for the full 18 months rather than the treat to clear strategy, which involves early cessation of treatment if Aβ PET is indicative of amyloid clearance), raising potential issues for patient safety and costs.

The ESCs noted the submission sought advice as to whether a separate MBS item is required for MRI brain scans to monitor for ARIA events associated with donanemab treatment, rather than using existing MBS item 63004 (Table MSAC 7a).

- The ESCs noted the department's advice that new MRI items specific to baseline scanning (Table MSAC 7b) and routine monitoring during treatment (MSAC Table 7c) are required due to current items, such as item 63004, not being suitable for detecting ARIA events.
- The ESCs noted that if MSAC advises that new MBS items are not required, then utilisation could be tracked by linking the PBS item for donanemab and the MBS item for MRI.

The ESCs noted that the Department's proposed new MRI item for monitoring during treatment specifies that the service is applicable not more than 4 times in a 12-month period (Table MSAC 7c). The ESCs noted a potential issue with the frequency restriction, as more than 4 MRIs may be required in a 12-month period if a patient has a significant ARIA event or has symptoms indicative of an ARIA. It is possible that item 63064 could be used for patients who are symptomatic. The ESCs agreed with the Department's proposed schedule fees but noted a potential for fee reduction for the new pathology items (*APOE* genetic testing, CSF biomarker testing) due to economies of scale.

The ESCs noted that the Department seeks advice whether a new MBS item is required for intravenous (IV) administration of donanemab, noting that there are limited MBS items available for IV drug administration including MBS items 13950 (for administration of antineoplastic agents) and 14245 (for administration of immunomodulating agents), which may not be directly applicable to the administration of donanemab. A separate or amended IV administration item may be required for non-admitted patients receiving the infusions.

Implementation

APOE genotyping

The ESCs noted that there are 4 member laboratories providing privately funded *APOE* genotyping according to the Royal College of Pathologists of Australasia, with unknown current throughput. The ESCs noted the department's advice that additional laboratories would need to be accredited to perform *APOE* genotype testing.

The ESCs noted that there is a need to disclose *APOE* status to patients. The ESCs considered that patients who are *APOE4* heterozygotes should be informed and provided with education of the associated risks of treatment (e.g., risk of ARIA events), to facilitate shared decision-making in clinical management.

Aβ PET scanning

The ESCs noted the department's advice that access to the Aβ-PET radiotracers necessary for the proposed Aβ-PET scan will present logistical challenges:

- As of 1 May 2025, there are 125 sites in Australia operating Medicare-eligible PET machines, the majority of which are in metropolitan or larger regional areas.
- The production of amyloid radiopharmaceuticals is currently limited to Cyclotek manufacturing facilities in Melbourne, Sydney and Brisbane, and a small number of hospital nuclear medicine departments with onsite cyclotrons.
- These radiopharmaceuticals have a short half-life of approximately 110 minutes, which may limit the geographic reach for timely delivery of the product across Australia. While this constraint is not unique to Aβ-PET radiotracers, it is a recognised challenge for PET services more broadly across Australia and is currently managed by the industry. The PSCR provided input from Cyclotek which stated that Aβ-PET radiotracers can be supplied for use within a 6-8-hour transport radius (either by air or road transport) and that its usage is not limited to the PET facilities that have on site radiotracer manufacturing capabilities.

The ESCs requested clarification on whether Aβ-PET radiotracers available in Australia are manufactured by extemporaneous compounding and therefore exempt from requiring regulation as claimed in the submission, or if they are manufactured by other methods which may require regulations to be in place. The ESCs requested the applicant to provide evidence that Aβ-PET radiotracers are appropriately regulated (or evidence that it is exempt from requiring regulation) in Australia that would support ongoing use as described in the submission.

The ESCs noted potential challenges for patients with early symptomatic AD to undertake Aβ PET.

CSF AD biomarker testing

The ESCs noted the department's advice that to ensure timely processing of patient samples, existing National Association of Testing Authorities (NATA)-accredited laboratories (2 Australian laboratories currently) would need to increase capacity and additional laboratories would need to be accredited to provide the service. In addition, a quality assurance program (QAP) would need to be established to ensure the reliability and reproducibility of results across laboratories.

The ESCs considered that CSF AD biomarker testing would most likely be offered to rural and regional patients due to likely capacity constraints for Aβ PET, which are more likely to be available in metropolitan centres.

Brain MRI

The ESCs noted the department's advice that there may be accessibility challenges to MRI machines and appointments, particularly for rural/remote patients.

Health system capacity

The ESCs noted the significant new resource use associated with the proposed PBS listing of donanemab treatment:

- The proposed MBS-funded tests required to access PBS-listed donanemab, including baseline brain MRI, *APOE* genotyping (to rule out *APOE4* homozygotes), Aβ PET brain scanning and CSF AD biomarker testing (to detect Aβ pathology), and other associated resource use if relevant (e.g., professional attendance, blood collection, CT scans, anaesthesia);
- Tests required to assess amyloid clearance (Aβ PET, at 24 and 52 weeks) and for monitoring (brain MRI) during donanemab treatment, and other associated resource use if relevant (e.g., professional attendance, CT scans, anaesthesia); and
- Costs associated with the administration of donanemab and management of adverse events.

The ESCs noted the department's concerns regarding the adequacy of the existing system capacity and the additional resources required (e.g., capital investments, memory clinics, infrastructure, health workforce with relevant expertise) to support the proposed MBS/PBS listings, as well the likely challenges for patients in rural/regional areas (e.g., inequitable access to treatment, under- or unnecessary treatment).

The ESCs considered that there is a very high risk of severe capacity constraints at several "pinch points" on the proposed new clinical management pathway, e.g., memory clinics, specialist physicians for diagnosis, brain MRI, PET scans, CSF sampling, IV infusion services, etc.

The ESCs advised that the implementation costs of the proposed MBS/PBS listings are highly uncertain but likely considerable, with immense opportunity costs arising from service pressures and disparities of access to the proposed technologies.

Other matters

The ESCs noted that the commentary reported that blood-based biomarker p-tau217 is a potential candidate for detecting Aβ pathology via a blood test, potentially reducing the need for either Aβ-PET or lumbar puncture for CSF AD biomarker testing in the near future. The ESCs noted that the Australian Dementia Network is currently running a trial of the pTau-217 blood biomarker test in primary care settings in Adelaide, Newcastle and north-eastern Melbourne.

The department noted that the FDA (Food and Drug Administration) have approved a blood-based biomarker to aid in diagnosing Alzheimer Disease, which measures two proteins, pTau217 and β-amyloid 1-42.[17] The department noted that the FDA approval was based on the test's correlation with the CSF AD biomarker testing only.

17. Applicant comments on MSAC's Public Summary Document

Lilly wishes to thank all of the healthcare professionals, professional societies, leadership bodies, patient organisations, consumers and broader industry for their support of our submission seeking reimbursement of amyloid pathology testing and *APOE* genotyping to inform treatment with Kisunla (donanemab). We are disappointed by MSAC's decision not to support the MBS

[17] https://www.fda.gov/news-events/press-announcements/fda-clears-first-blood-test-used-diagnosing-alzheimers-disease.

listing of these important diagnostic tools. Lilly is working to fully understand the implications of this outcome and potential next steps.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website.