MSAC Application 1738

Two testing options to detect early-stage Alzheimer's Disease, to determine eligibility for PBS subsidised lecanemab treatment

PART 1 – APPLICANT DETAILS

1. **Applicant details (primary and alternative contacts)**

Corporation/partnership details

Corporation name: Eisai Australia Pty Ltd

Business trading name: Eisai Australia Pty Ltd

Primary contact name: REDACTED

Primary contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

2. **(a) Are you a consultant acting on behalf on an applicant?**

☐ Yes
☒ No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

Not applicable

3. **(a) Are you a lobbyist acting on behalf of an Applicant?**

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

Not applicable

(c) Have you engaged a consultant on your behalf?

☐ Yes
☒ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. **Application title**

   Two testing options to detect early-stage Alzheimer's Disease, to determine eligibility for PBS subsidised lecanemab treatment

5. **Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)**

   Alzheimer's Disease (AD) is a progressive, neurodegenerative disorder, characterized by an unrelenting decline in cognition and behavioural disturbances, that result in the person's inability to perform usual daily living activities. AD is the most common cause of dementia, accounting for 60-70%[1] of all cases.

   The pathophysiology is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, followed by gradual atrophy of the entire brain. The main neuropathological hallmarks are extracellular senile (neuritic) plaques containing aggregated amyloid beta (Aß) peptides and intraneuronal neurofibrillary tangles composed of abnormal hyperphosphorylated Tau protein.

   The ultimate outcome is a loss of cognition and memory. Early symptoms include difficulty with recent memories, apathy, and depression. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavioural changes, and difficulty speaking, swallowing, and walking. In the final stages, individuals are bedridden and need full-time care.

6. **Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)**

   The proposed two medical services are for the protein biomarker tests, Aß positron emission tomography (PET) and cerebrospinal fluid (CSF), either of which could be used to detect the presence of Aß pathology in patients with AD. A positive Aβ PET scan or CSF biomarker test result will be used to determine patient eligibility to the drug treatment, lecanemab.

   Pharmaceutical Benefits Schedule (PBS) subsidy will also be sought for lecanemab (brand name TBC), an anti-Aβ protofibril antibody, for the treatment of mild cognitive impairment (MCI) due to AD or mild AD dementia with confirmed presence (via Aß PET or CSF) of amyloid pathology.

   Diagnosis of AD in Australia, is predominantly based on clinical findings and a brain scan with computerised tomography (CT) or magnetic resonance imaging (MRI). This clinical diagnosis approach, without PET or CSF evidence of brain amyloid, is only ~70% accurate in the MCI and mild dementia phase compared to the "gold standard" neuropathology examination.

7. **(a) Is this a request for MBS funding?**

   ☒ **Yes**
   ☐ **No**

   (b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

   ☐ **Amendment to existing MBS item(s)**
   ☒ **New MBS item(s)**

   (c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service/technology:

   Not applicable

   (d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

   Not applicable

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and/or population)
☐ A new item for a specific single consultation item
☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

Not applicable

8. **What is the type of medical service/technology?**

☐ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☒ Co-dependent technology
☐ Hybrid health technology

9. **For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:**

☐ To be used as a screening tool in asymptomatic populations
☐ Assists in establishing a diagnosis in symptomatic patients
☐ Provides information about prognosis
☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

10. **Does your service rely on another medical product to achieve or to enhance its intended effect?**

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

11. **(a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?**

☐ Yes
☒ No

(b) If yes, please list the relevant PBS item code(s):

Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: Not available at the time of submitting this application form.

Generic name: Lecanemab

12. **(a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?**

Not applicable

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

Not applicable

(d) Are there any other sponsor(s) and/or manufacturer(s) that have a similar prosthesis or device component in the Australian marketplace which this application is relevant to?

Not applicable

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Not applicable

13. **Please identify any single and / or multi-use consumables delivered as part of the service?**

Key consumables for Aβ PET

Radiopharmaceutical for Aβ PET imaging of the brain, for intravenous injection

Key consumables for CSF Aβ and Tau assays

Immunoassay kits and reagents, low binding tubes,

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer, or any other type of therapeutic good, please provide details

Aβ PET imaging

Amyloid beta (Aβ) PET offers direct confirmation of the presence of Aβ brain pathology. PET is a minimally invasive diagnostic imaging technique used to distinguish normal from abnormal tissue in numerous indications including neurologic disorders. It is the only antemortem technique that can directly confirm the presence of brain Aβ pathology.

There are currently 85 Medicare eligible PET scanning facilities in Australia. Aβ PET scanning is not currently funded on the MBS[2].

Aβ PET imaging employs a radioisotope labelled tracer that is intravenously administered and travels to the brain to selectively bind Aβ aggregates. As the radiolabel tracer decays, the positron emissions from the decay are captured by the PET scanner camera. The relative differences in the rate of the tracer decay within the different anatomical regions of the brain provide information that can be used to create an image which informs on the density and location of the amyloid plaques within the brain.

Cyclotek[3] are the only company that produce Aβ PET radiotracers commercially in Australia and New Zealand. Cyclotek has validated the manufacture of the three Aβ radiopharmaceuticals, 18F-florbetaben (Neuraceq®), 18F-florbetapir (Amyvid®) and 18F-flutemetamol (Vizamyl®) (Table 1). These are also available through the Special Access Scheme. They have regulatory approval in jurisdictions US and Europe.

Other producers of Aβ PET radiopharmaceuticals in Australia include hospital nuclear medicine departments with onsite cyclotrons. Manufacturing standards across local producers of Aβ PET tracers can vary as local hospitals do not require a Good Manufacturing Practice license, which is mandatory for commercial companies. Another radiopharmaceutical, 18F-flutafuranol or NAV4694, is produced by Austin Health Melbourne, Sir Charles Gardner Hospital Perth and the Royal Brisbane Hospital. It is used for research and currently has limited clinical use although it is under development for wider commercial use. The use of the NAV4694 tracer may be necessary to allow for equitable access in Australia as the other FDA- approved tracers are not currently manufactured in Western Australia and can only be shipped to South Australia and the eastern states. The applicant sponsor is currently having discussions with clinical experts to obtain equivalence data for NAV and 18F-florbetaben /18F-florbetapir on the same patients.

Table 1: Aβ PET imaging radioisotope labelled tracer

Type of therapeutic good	Product details	Commercial availability	Brand Name	Sponsor's Name
Diagnostic radiopharmaceutical for PET	11C [2-(4'-[11C] methylaminophenyl)-6-hydroxy-benzothiazole] ("11C Pittsburgh compound B [PiB])	Not applicable	Not applicable	Not applicable
Diagnostic radiopharmaceutical for PET	18F-florbetapir for iv injection	Commercially available in some jurisdictions outside of Australia	Amyvid®	Eli Lilly
Diagnostic radiopharmaceutical for PET	18F-florbetaben for iv injection	Commercially available in some jurisdictions outside of Australia	Neuraceq®	PIRAMAL Imaging

Type of therapeutic good	Product details	Commercial availability	Brand Name	Sponsor's Name
Diagnostic radiopharmaceutical for PET	18F-flutemetamol for iv injection	Commercially available in some jurisdictions outside of Australia	Vizamyl®	GE Healthcare
Diagnostic radiopharmaceutical for PET	18F-flutafuranol r for iv injection (NAV4694)	Commercially available in some jurisdictions outside of Australia	Not applicable	Cerveau Technologies have acquired licensing rights that cover Australia

CSF AD Aβ and Tau CSF biomarker assay kits

CSF AD biomarker testing offers confirmation of the presence of Aβ and tau (including phospho-tau) brain pathology. CSF AD biomarker testing is performed by in vitro immunoassays. A CSF sample is obtained from the patient by lumbar puncture (LP) using a standardised collection procedure. Levels of specific biomarkers (amyloid β42 peptides, total tau and phosphorylated tau) in the sample are then quantified by in vitro immunoassay methods, and amyloid positivity or negativity determined by cut-offs which have been validated against Aβ PET.

Testing for CSF AD biomarkers is therefore an alternative to Aβ PET to confirm Aβ pathology.

There are a number of commercial CSF AD biomarker assay kits (immunoassay kits for amyloid isoforms, total tau and phosphorylated-tau) that are approved in jurisdictions outside of Australia (examples are shown in Table 2. As per a previous application, CSF AD biomarker testing is currently offered for a non-rebated fee by at least one National Association of Testing Authorities Australia (NATA)/ International Laboratory Accreditation Cooperation (ILAC) accredited diagnostic laboratory (National Dementia Diagnostics Laboratory (NDDL) at the Florey Institute)[4] (see: https://www.florey.edu.au/science-research/scientific-services-facilities/nationaldementia-diagnostics-laboratory).

Table 2: Commercial CSF AD biomarker assay kits approved outside of Australia

Type of therapeutic good	Product details	Commercial availability	Brand Name	Sponsor's Name
In vitro diagnostic test	Enzyme linked immunoassay for quantitative determination of AD biomarkers (amyloid and tau proteins) in human cerebrospinal fluid (CSF).	ADx- EUROIMMUN • ELISA for BetaAmyloid (1-42) • ELISA for BetaAmyloid (1-40) • ELISA for total tau • ELISA for P-tau	EUROIMMUN	Commercially available in some jurisdictions outside of Australia [5] https://www.euroimmun.com/
In vitro diagnostic test	Quantitative fluorimetric xMAP® microbead-based multiplex sandwich enzyme linked immunoassay (ELISA) for the simultaneous quantification of phosphorylated tau (P-tau(181P)), tau, and ß-amyloid (1-42) (Aß(1-42)) in human CSF. For research use only. Not for use in diagnostic procedures.	INNO-BIA AlzBio3 xMAP	Innogenetics	Commercially available in some jurisdictions outside of Australia https://search.cosmobio.co.jp/cosmo_search_p/search_gate2[6]/docs/IGT_/80584.20090219.pdf

Type of therapeutic good	Product details	Commercial availability	Brand Name	Sponsor's Name
In vitro diagnostic test	ElectroChemiLumines cence sandwich Immunoassay (ECLIA) for the in vitro quantitative determination of AD biomarkers (amyloid; tau proteins) in human Cerebrospinal Fluid (CSF) Electrochemiluminescence assay using the Cobas e610 instrument	Elecsys® β-Amyloid (1-42) CSF Elecsys® Phospho-Tau (181P) CSF Elecsys® Total -Tau CSF	Roche Diagnostics	Commercially available in some jurisdictions outside of Australia[7] https://diagnostics.roche.com/global/en/products/product-category/neurology.html
In vitro diagnostic test	Immunoassay (using immunoreaction cartridges) intended for the quantitative measurement AD biomarkers (amyloid; tau proteins) in CSF, based on CLEIA (ChemiLuminescent Enzyme ImmunoAssay) technology Intended to be used in conjunction with Lumipulse G β- Amyloid 1-40 assay	Lumipulse G β-Amyloid 1-42 Lumipulse G β-Amyloid 1-40 Lumipulse G Ptau 181 Lumipulse G total tau	Fujirebio	Commercially available in some jurisdictions outside of Australia[8] https://www.fujirebio.com/en/products-solutions/neurodegeneration

(b) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

(c) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

No

15. **(a) If not listed on the ARTG, is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?**

☒ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☐ No

Radiopharmaceuticals for Aβ PET

In Australia, there are currently, no radiopharmaceuticals for Aβ PET approved by the TGA. The Applicant understands that radiotracers for Aβ PET scanning do not currently require TGA approval under "extemporaneous compounding" exemption.

CSF AD Aβ and Tau CSF biomarker assay kits
In addition, although the following Roche Diagnostics CSF AD biomarker testing kits were approved by the TGA (April 2020):
   o Elecsys® β-Amyloid(1-42) CSF,
   o Elecsys® Phospho-Tau (181P) CSF
   o Elecsys® Total -Tau CSF

It is not possible to determine the specific ARTG numbers unless the product name is on the ARTG.

- Class 1, 2 and 3 IVDs do not require the product trade name to be contained within the ARTG listing so the information provided does not necessarily align with an entry.
- Multiple products with the same GMDN and manufacturer could be within the one ARTG listing
- No requirement for these class of devices for the ARTG number to be on the product packaging so cannot check via this method

The three above assay kits are class 3 IVDs and therefore no ARTG can be determined at this stage. The applicant proposes to contact the sponsor and confirm the ARTG number as part of the submission.

16. **If the therapeutic good is <u>not ARTG listed</u>, is the therapeutic good in the process of being considered by TGA?**

As far as the Applicant is aware, the TGA is not in the process of considering an application for an Aβ PET tracer or other CSF biomarker assay kit.

(b) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

☐ Yes (please provide details below)
☒ No

As far as the Applicant is aware, no application to the TGA is currently being prepared for any Aβ PET tracer or other CSF biomarker assay kit.

As per a previous application, the assumption in this application is that, where required, TGA approval of Aβ PET radiolabelled tracer(s) and CSF Aβ and tau biomarker assay kits(s) for clinical use will concur with the TGA approval of lecanemab and reimbursement submission for lecanemab.

PART 4 – SUMMARY OF EVIDENCE

17. Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Phase 1 Trial: A multicenter, randomized, double-blind, placebo-controlled, clinical study with single dose and multiple dose components	• Logovinsky V, Satlin A, Lai R, et al. Safety and tolerability of BAN2401--a clinical study in Alzheimer's disease with a protofibril selective Abeta antibody. Alzheimers Res Ther. 2016;8(1):14. • NCT01230853 ClinicalTrials.gov. A Randomized, Double-blind, Placebo-controlled, Combined Single Ascending Dose and Multiple Ascending Dose Study to evaluate the safety and tolerability of lecanemab.	Assessed safety and tolerability of single IV infusions of lecanemab at sequentially ascending doses in mild to moderate AD from baseline to Day 180 post-dose (Single ascending study) and at 4 monthly IV infusions of lecanemab at sequentially ascending doses from baseline to Day 264 post-dose (Multiple ascending study)	https://clinicaltrials.gov/ct2/show/NCT01230853.[9]	2016
2.	Phase 2b Trial: multinational, multicenter, double-blind, placebo-controlled, parallel-group clinical study that compared the efficacy of several dosing regimens of lecanemab to that of placebo. The study employed a Bayesian design with response adaptive randomization to assign patients via computer to different dosing regimens of lecanemab or to placebo. Patients maintained their assigned dose throughout the trial.	• Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Abeta protofibril antibody. *Alzheimers Res Ther.* 2021;13(1):80. • ClinicalTrials.gov. A Study to Evaluate Safety, Tolerability, and Efficacy of Lecanemab in Subjects With EarlyAlzheimer's Disease. • Wong W. Economic burden of Alzheimer disease and managed care considerations. *Am J Manag Care.* 2020;26(8 Suppl):S177-s183.	854 randomized subjects were treated (lecanemab, 609; placebo, 245), and a total of 382 participants treated with lecanemab completed treatment, while 205 participants treated with lecanemab discontinued treatment (36.0%).	https://clinicaltrials.gov/ct2/show/record/NCT01767311?term=lecanemab&draw=2&rank=3[10]	2020 and 2021. Accessed November 2022

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	Extension Phase Study Design: This study was an extension to the Phase 2 study described.	ClinicalTrials.gov. A Study to Evaluate Safety, Tolerability, and Efficacy of Lecanemab in Subjects with Early Alzheimer's Disease.	The primary endpoint was to determine the long-term safety and tolerability of lecanemab in patients with early AD. The secondary endpoint evaluated treatment benefit in brain amyloid levels (measured by amyloid PET) at the end of the Core study was maintained in participants throughout the extension phase All AEs and SAEs were evaluated	https://clinicaltrials.gov/ct2/show/record/NCT01767311?term=lecanemab&draw=2&rank=3. [11]	Published 2021. Accessed November 2022
4.	Clarity AD was a global confirmatory was a Phase 3 randomized, double-blind, placebo-controlled clinical study to evaluate the long-term efficacy and safety of biweekly IV lecanemab 10 mg/kg in 1,795 people with early AD. The treatment group was administered a dosage of 10 mg/kg bi-weekly of lecanemab, with participants allocated in a 1:1 ratio to receive either placebo or lecanemab.	NCT03887455: A Study to Confirm Safety and Efficacy of Lecanemab in Participants with Early Alzheimer's Disease (Clarity AD).	Primary outcome measures at month 18: • Change from baseline in CDR-SB = Clinical Dementia Rating Sum of Boxes Key secondary outcome measures at month 18: • Change from baseline in the amyloid PET SUVr (Standard uptake-value ratio) composite • Change from baseline in ADCOMS = Alzheimer's Disease Composite Score; • Change from baseline in ADAS-cog 14 = Alzheimer's Disease Assessment Scale–Cognitive Subscale 14	https://clinicaltrials.gov/ct2/show/NCT03887455 [12]	Baseline data has been published in 2021. Full dataset is pending publication.

18. Identify <u>yet-to-be-published</u> research that may have results available in the near future (that could be relevant to your application).

	Type of study design	Title of research	Short description of research	Website link to research	Date
1.	AHEAD 3-45 Study: A Placebo-Controlled, Double-Blind, Parallel-Treatment Arm, 216 Week Study to Evaluate Efficacy and Safety of Treatment With BAN2401 in Subjects With Preclinical Alzheimer's Disease and Elevated Amyloid (A45 Trial) and in Subjects With Early Preclinical Alzheimer's Disease and Intermediate Amyloid (A3 Trial)	NCT04468659: A Study to Evaluate Efficacy and Safety of Treatment With Lecanemab in Participants With Preclinical Alzheimer's Disease and Elevated Amyloid and Also in Participants With Early Preclinical Alzheimer's Disease and Intermediate Amyloid	Is treatment with lecanemab superior to placebo on change from baseline of the Preclinical Alzheimer Cognitive Composite 5 at 216 weeks of treatment (A45 Trial) and is treatment with lecanemab superior to placebo in reducing brain amyloid accumulation as measured by amyloid PET at 216 weeks of treatment (A3 Trial).	https://clinicaltrials.gov/ct2/show/NCT04468659	

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies/organisations representing the health professionals who provide the service. For <u>MBS-related applications</u> ONLY, please attach a brief 'Statement of Clinical Relevance' from the most relevant college/society.**

    The Australasian Association of Nuclear Medicine Specialists (AANMS)

    Australian Diagnostic Imaging Association (ADIA)

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    Not applicable

21. **List the consumer organisations relevant to the proposed medical service (noting there is <u>NO NEED</u> to attach a support letter at the 'Application Lodgement' stage of the MSAC process):**

    Dementia Australia

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce <u>similar</u> products relevant to the proposed medical service:**

    Cyclotek

    T +61 3 9467 4966

    enquiries@cyclotek.com

23. **Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:**

    REDACTED

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease (in terms of both morbidity and mortality):

AD is a progressive, degenerative neurocognitive disorder, characterized by an insidious and unrelenting decline in cognition, as well as behavioural disturbances, that result in the person's inability to perform usual activities of daily living. AD is the most common cause of dementia, accounting for 50% to 75% of all cases. Dementia is a syndrome characterized by disturbance of multiple brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment, with no disturbance in consciousness. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. Three stages of AD proposed by the National Institute on Aging and the Alzheimer's Association[13] are shown in Figure 1:

- preclinical Alzheimer's disease;
- mild cognitive impairment (MCI) due to Alzheimer's disease;
- dementia due to Alzheimer's disease.

Figure 1: Stages of AD
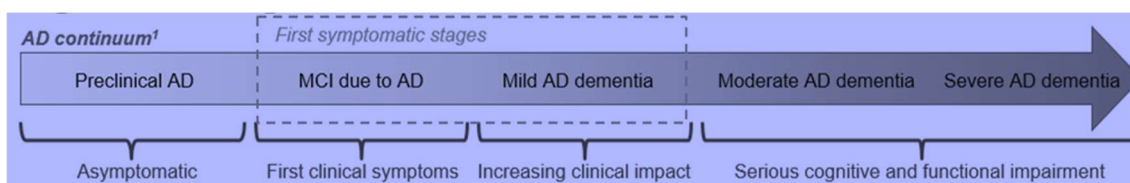
AD pathophysiology

The pathophysiology of AD is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, followed by gradual atrophy of the brain, excluding the cerebellum. The main neuropathological hallmarks of AD are extracellular senile (neuritic) plaques containing aggregated amyloid beta peptides and intraneuronal neurofibrillary tangles (NFTs) composed of abnormal hyperphosphorylated Tau protein. Although the pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome is not yet fully elucidated, the leading hypothesis is the "amyloid cascade." This hypothesis proposes that the accumulation of amyloid beta, which results from an imbalance between amyloid beta production and amyloid beta clearance in the brain, is the driving force behind the AD process. Senile plaques and neurofibrillary tangles prompt the injury and death of neurons, and consequently, memory loss and behavioural symptomatic changes. Inflammation within the brain, including increased reactivity of the resident microglia towards amyloid deposits, has been implicated in the pathogenesis and progression of AD.

The ultimate debilitating outcome of Alzheimer's disease is a progressive loss of cognition and memory. Early symptoms include difficulty with recent memories (such as conversations, names, or events), apathy, and depression. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavioural changes, and difficulty speaking, swallowing, and walking. In the final stages of the disease, individuals are bedridden and need full-time care.

Mortality and morbidity

The risk of dementia increases with stages of AD progression [14] The lifetime risk of AD dementia for a 60-year-old person in the normal state has been estimated to be 20.1% among females and 13.9% among males. However, that risk increases for patients with Aβ deposition and neurodegeneration, to 41.9% among females and 33.6% among males, and, for patients with MCI and Aβ pathology, lifetime risk is ≥90%.32 A Japanese study found that the rate of progression to MCI among amyloid-positive subjects with preclinical AD was 10.4% per year,[15] and that the annual rate of progression to dementia among amyloid-positive patients with MCI due to AD was 20.7%.[16]

Globally, dementia (all-cause) is the fifth leading cause of death, with 4.4% of all deaths attributable to dementia in 2016.[17] Deaths due to dementia have steadily increased over time, partly due to population growth and population aging, more than doubling from 1990 to 2016. AD-related deaths have also risen. An analysis of AD mortality in Europe found that deaths from AD among patients aged ≥50 years more than doubled from 1994 (41,255 deaths) to 2013 (86,822).36 The age-standardized mortality rate for deaths cause by AD in Europe was 45.2 per 100,000 in 2013.36 In the US in 2017, AD accounted for 46% of all deaths attributed to dementia (121,404 deaths due to AD of 261,914 deaths due to dementia).[18]Median survival among persons with AD dementia has been estimated to be approximately 7 years from presentation with cognitive decline (non-memory related cognitive decline typically presents in the mild to moderate stage);[19] this estimate was based on an analysis of data from one geographic area in England).[20] AD is the leading cause of cognitive impairment and dementia in older individuals (aged ≥65 years) throughout the world. [21]AD follows a prolonged, progressive disease course that begins with pathophysiological changes in the brains of affected individuals, including the accumulation of toxic species of amyloid-β (Aβ) and the development of neurofibrillary tangles of hyperphosphorylated tau protein, years before any clinical manifestations are observed.[22]

It is estimated that there are currently between 397,923 (AIHW 2022) and 487,500 Australians living with dementia, and on the current trajectory this number could increase to almost 1.1 million by 2058 (Dementia Australia 2020). Dementia is the second-leading cause of death in Australia, resulting in 14,500 deaths (9.6% of all deaths) in 2020 (AIHW 2022). It is also estimated that almost 1.6 million people in Australia are involved in the care of someone living with dementia (Dementia Australia 2022). These estimates vary because there is no single authoritative data source for deriving dementia prevalence in Australia, and different approaches are used to generate estimates.

Alzheimer's Disease (AD) may contribute to 60-70% of dementia cases worldwide (WHO 2022). Based on the dementia prevalence estimates (AIHW 2022, Dementia Australia 2022) and on the anticipated contribution of AD to these figures (WHO 2022), there could be between 238,754 and 341,250 Australians currently living with AD.

Data from five multicenter studies from multiple countries have demonstrated a high prevalence of AD with clinically diagnosed MCI using the International Working Group-1 (IWG-1), IWG-2 and NIA-AA criteria. Based on the IWG criteria, 53% (IWG-1) and 40% (IWG-2) of subjects with MCI were identified as having AD; three-year progression rates were 50% (IWG-1 criteria) in persons with prodromal (early signs or symptoms of an illness or health problem that appear before the major signs or symptoms start) AD versus 21% without prodromal AD, and 61% (IWG-2) with prodromal AD versus 22% without prodromal AD. Based on NIA-AA criteria, 46% of subjects with MCI were classified as being in the "high likelihood AD" group.[23]; and the three-year progression rate was 59% (compared to subjects with amyloid pathophysiology, suspected non-AD pathophysiology, and a low-likelihood AD group [22%, 24%, and 5%, respectively]). Other research has examined etiologic diagnoses of AD in MCI, finding that 75% of MCI subjects had an aetiology of AD (using 2011 NIA-AA criteria), while the remainder were classified with aetiologies such as cerebrovascular dementia and Lewy-body dementia.[24]

The incidence of MCI has been examined in a comprehensive systematic review of studies in Europe, the Americas, and Australia (important to note: the studies used a variety of diagnostic criteria). A meta-analysis found that incidence rates rose from 22.5 to 60.1 per 1000 person-years with increasing age, but with substantial heterogeneity in incidence estimates due to methodological and population sample characteristics in the included studies. Analyses resulted in MCI incidence of 22.5 (95% CI: 5.1, 51.4) per 1000 person-years for ages 75-79, 40.9 (95% CI: 7.7, 97.5) for ages 80-84, and 60.1 (95% CI: 6.7, 159.0) for ages 85 and older.[25]

Burden of disease

There are currently no disease modifying treatments (DMTs) available for treating AD. Current treatments are for symptomatic relief only, as shown in Table 3.

Table 3: Current AD treatments (symptomatic relief)

	Acetylcholinesterase Inhibitors (AChEI)	NMDA Antagonists	Behavioural Therapies
Therapeutic mechanism	Slows degradation of acetylcholine, thus increasing the effective concentration to provide symptomatic relief	Blocks sustained, low-level activation of NMDA receptor without inhibiting normal function of the receptor	Treats neuropsychiatric symptoms and behavioural disturbances (e.g. anxiety, depression, agitation)
Molecule	Donepezil, rivastigmine, galantamine	memantine	Quetiapine, olanzapine, escitalopram, risperidone
AD indication	Mild to moderately severe AD	Moderately severe AD	Not indicated for AD
PBS listed for AD	Yes	Yes	No

25. **Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):**

The application proposes two services for inclusion on the Medicare Benefits Schedule (MBS), either of which could be used to determine whether a patient with a clinical diagnosis of early-stage Alzheimer disease (AD) would be eligible for the co-dependent drug, lecanemab on the PBS, by confirming the presence of amyloid deposition in the brain, and as such, Alzheimer disease pathology as the underlying cause of the condition.

How the patient is managed and referred

In Australia, diagnosis of AD is predominantly based on clinical findings and a brain scan with computerised tomography (CT) or magnetic resonance imaging (MRI). This clinical diagnosis approach, without PET or CSF evidence of brain amyloid, is only 70% accurate in the mild dementia phase compared to the "gold standard" neuropathology examination[26] .It is not reliable in the MCI phase as only 50-60% of individuals with MCI develop AD on follow-up or have AD findings on neuropathology. Consequently, clinical diagnosis is usually made when an individual has progressed to dementia. Therefore, clinical diagnosis alone is not sufficiently accurate to identify persons with brain amyloid, especially in the MCI phase of early-stage AD when a disease modifying therapy is most beneficial. There are, however, reports from memory clinics across Australia that patients are increasingly being diagnosed at the prodromal stage, although the vast majority of the diagnosis are in the dementia stage.

There is currently no single test to identify AD. The diagnosis is made only after careful clinical consultation. According to the RACGP's *Clinical practice guidelines and principles of care for people with dementia in Australia*, GPs are recommended to undertake an initial assessment for a person suspected of having dementia. This includes:

- history taking from the person and if possible, from a person who knows the person well (such as family members or carers)
- cognitive and mental examination with a validated instrument (such as the Mini-Mental State Examination (MMSE), GP assessment of cognition (GPCOG), Rowland Universal Dementia Assessment Scale (RUDAS) for people from culturally and linguistically diverse backgrounds or the

Kimberley Indigenous Cognitive Assessment (KICA-Cog) for Aboriginal or Torres Strait Islander people living in rural or remote areas)
- physical examination and blood tests
- brain imaging; CT or MRI (where necessary)
- review of current medication use
- consideration of other causes, such as depression, delirium, thyroid disease or vitamin deficiency (Guideline Adaptation Committee 2016).

If dementia is a suspected diagnosis, the clinical guidelines state that best practice is for GPs to make a referral to memory assessment specialists (such as geriatricians or psycho-geriatricians) or services (such as memory clinics) for a comprehensive assessment. The Australian Dementia Network (ADNeT) has a list of **REDACTED** memory clinics in Australia (Find a Memory Clinic or Cognitive Decline Assessment Service - Australian Dementia Network). Most of the clinics use the new memory clinic guidelines ADNeT Memory and Cognition Clinic Guidelines - Australian Dementia Network and are now part of a clinical quality registry (As of December 2021, the ADNeT Registry had **REDACTED** participating sites).

The aim of the comprehensive assessment is to gather information about changes in behaviour, functional capacity, psychosocial issues and relevant medical conditions to allow for a diagnosis to be made.
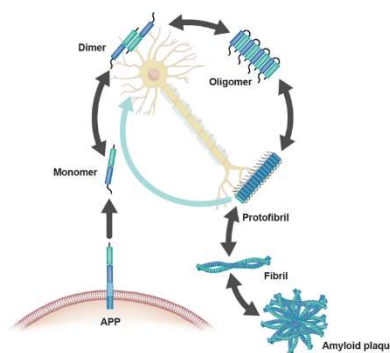

Figure 2: amyloid aggregation pathway[27]

Who to test:

Lecanemab, a humanized IgG1 monoclonal antibody that binds to soluble Aβ protofibril aggregates (as seen in Figure 2), is expected to be used for the treatment of early AD (Mild cognitive impairment (MCI) due to AD and mild AD dementia stage of disease) with confirmed amyloid burden. Treatment with lecanemab should be initiated for the treatment of patients with early AD.[28]

In current Australian practice, there is no single test to identify AD. The diagnosis is made only after careful clinical consultation. Testing to detect amyloid pathology is not funded by the Commonwealth for patients with AD. Patients with a clinical diagnosis of MCI suspected to be due to AD are currently observed initially followed by symptom relieving drugs (which are currently only indicated for mild and/or moderate dementia stages, not MCI). There are currently no disease modifying treatments (DMTs) available for treating AD.

Target patients for lecanemab treatment are those with early-stage AD, composed of MCI due to AD/prodromal AD and mild AD dementia. The proposed services are therefore intended to identify patients with amyloid brain pathology consistent with the patient population in whom the drug has been shown to be effective, by confirming the presence of what is considered to be the target for the drug's mode of action. It is proposed that the testing to detect AD/amyloid pathology be conducted sequentially upon receiving a clinical diagnosis and before any treatment has begun.

In the clinical trials of lecanemab, the patients were specifically defined as having mild cognitive impairment (MCI) due AD or mild AD dementia. These diagnoses require evidence of AD related pathology, specifically amyloid PET or cerebrospinal fluid (CSF) evidence of brain beta-amyloid. As per a

previous application 1643, the Applicant proposes that that the target patient population be referred to as "early-stage AD" for the purposes of the PICO application form.

The clinical features of the early-stage AD would require confirmation by a specialist. This can be completed once a GP has referred a patient to specialist service (e.g., memory clinics) or a specialist clinician (geriatrician, neurologist, psycho-geriatrician or psychiatrist, experienced in the diagnosis and management of patients with cognitive impairment disorders or dementia, including Alzheimer's disease), forwarding record of brief clinical history, investigation results, past history of drug lists and MMSE and/or other supporting assessments.

High dose lecanemab has been shown to reduce beta-amyloid (Aβ) plaque burden on amyloid positron emission tomography (PET) and, concomitantly, slows clinical AD disease progression, as measured by a range of cognitive and functional endpoints, in patients diagnosed with MCI due to AD or mild AD dementia, with confirmed amyloid brain pathology.[29]

PART 6b – INFORMATION ABOUT THE INTERVENTION

26. **Describe the key components and clinical steps involved in delivering the proposed medical service/technology:**

Please note that the following steps have been taken from the previous application 1643 as they are completely applicable:

Aβ PET

Delivery of Aβ PET scanning can be broken down into 4 key "phases". These are:

(1) 18F-tracer preparation and administration;
(2) image acquisition;
(3) image reconstruction and interpretation; and
(4) documentation and reporting.

Radiotracer preparation and administration

18F radiotracers are likely to be either sourced from a commercial supplier or prepared inhouse in facilities with a cyclotron and radio-pharmacy capability. The 18F radiotracer for Aβ PET is administered intravenously prior to scanning. Aseptic technique and radiation shielding are required to withdraw and administer the tracer. Although the 18F radiotracers used for Aβ PET share a common imaging target and similar imaging characteristics, amyloid tracers can differ in their tracer kinetics, specific binding ratios, and optimal imaging parameters and hence will have different recommended injected doses, times to initiate imaging after injection, and scan durations.

Image acquisition

Before scanning, a patient should empty their bladder for maximum comfort during the study. The patient should be positioned in a supine position, with the patient's brain in a single field of view. Reducing head movement with tape or other flexible head restraints may be employed. The radiotracer should be injected as a single intravenous slow bolus in a total volume of 10 mL or less. The catheter should be flushed with at least 5–15 mL of 0.9% sterile sodium chloride to ensure full delivery of the dose.

Images should be acquired in 3-dimensional mode with appropriate data corrections and reconstructed using attenuation correction with typical trans-axial pixel sizes of 2– 3 mm and a slice thickness of 2–4 mm. The patient should be advised to hydrate and void after the scanning session to diminish radiation exposure.

PET scanning radiation dose:

According to the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European Association of Nuclear Medicine (EANM) and clinical practice guidelines, 18F-florbetapir, 18F-flutemetamol and 18Fflorbetaben tracers offer a reasonable compromise between radiation exposure following "as low as reasonably achievable (ALARA)" principles and image quality.

PET image reconstruction and interpretation:

It is important to note that the objective of the image interpretation is to estimate β-amyloid plaque density in brain grey matter, not to make a clinical diagnosis. Image interpretation is performed independently of a patient's clinical features and relies upon the recognition of unique image features.

The specific criteria for Aβ PET image interpretation may differ among available radiotracers. It is therefore vital that images should be interpreted only by readers who have successfully completed the appropriate training provided by the manufacturer of the radiotracer being used. However, the following general principles are applied.

Images are designated as either "amyloid-positive" or "amyloid-negative" based on the visual assessment of tracer uptake in the grey matter. The Centiloid Project was initiated to derive a standardised quantitative amyloid imaging measurement scale, based upon normalisation of data from the 18F-tracers to that of PiB. In this linear scale, young controls (≤ 45 years) have a mean of zero Centiloid units (CL) and typical mild to moderate AD patients score on average 100 CL [10]. The data set used to determine PiB Centiloids is freely available on the Global Alzheimer Association Interactive Network website (GAAIN; http://www.gaain.org), together with standardised cortical and whole cerebellum volume of interest (VOI) templates. (Battle et al, EJNMMI Res, 2018; 8:107)

Documentation and reporting

Aβ PET results should be interpreted independently of clinical information, but the final report may integrate scan findings and clinical information and suggest a final or differential diagnosis and patient management plan. Commenting on any correlation with other available imaging data may be helpful to the referring physician.

General recommendations on nuclear medicine reports are provided in the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Procedure Standard on General Nuclear Imaging and the American College of Radiology (ACR) Practice Guideline for Communication: Diagnostic Radiology.

CSF AD biomarker testing

There are a number of immunoassay kits for the assessment of CSF AD biomarker proteins such as amyloid β42 peptide, total tau and phosphorylated tau that are approved and commercially available outside of Australia. Examples have been provided earlier in Table 2.

Specimen collection and pre-analytical handling

A CSF sample is obtained from the patient by lumbar puncture (LP) procedure. This is covered by MBS items 39000/21945/23010. For CSF AD biomarker testing, it is important that the CSF specimen collection and pre-analytical handling follow a highly standardised procedure as specified by the analysing laboratory or as recommended by the manufacturer of the assay kit being used.

For example, for standardising results, there may be specific requirements regarding best time of day for specimen collection, the level at which the lumbar puncture should be performed, the type of collection tube that should be used, specimen handling (e.g., centrifugation, mixing procedure; tube filling volume used, rejection of specimen due to haemolysis), conditions for shipment to the testing laboratory, conditions for storage and thawing. All the different commercial assay kit systems are based on in vitro immunoassay principles. The assay procedures should be followed according to the kit manufactures specifications, following appropriate calibration and quality control procedures.

All the commercial kits have been validated against Aβ PET by the manufacturers, with the Roche Elecsys assays validated by the National Dementia Diagnosis Laboratory (NDDL) to generate pre-defined cut-offs for amyloid positivity and negativity. The Elecsys test kits provide pre-defined cut-offs for amyloid positivity and negativity. The NDDL are using cut-offs set by Roche diagnostics and have a QC process in place.

Treatment and mechanism of action of codependent drug intervention lecanemab [30]

Lecanemab is an investigational anti-amyloid beta (Aβ) protofibril antibody for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD (collectively known as early AD) with confirmed presence of amyloid pathology in the brain (confirmed via Aß positron emission tomography (PET) and cerebrospinal fluid (CSF)).

Lecanemab preferentially binds with highest affinity to large soluble Aβ protein aggregates, known as protofibrils, while maintaining high affinity for fibrillar Aβ that are a major component of Aβ plaques. The accumulation of Aβ plaques in the brain is a defining pathophysiological feature of AD. Lecanemab reduces Aβ plaques, as evaluated in its Phase 2 and Phase 3 trials.

Clarity AD was a global confirmatory Phase 3 placebo-controlled, double-blind, parallel-group, randomized study in 1,795 people with early AD. Lecanemab met the primary endpoint (CDR-SB: Clinical Dementia Rating-Sum of Boxes - a numeric scale used to quantify the various severity of symptoms of dementia) and all key secondary endpoints with highly statistically significant results. Lecanemab treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months by 27%, which represents a treatment difference in the score change of -0.45 (p=0.00005) in the analysis of Intent-to-treat (ITT) population. Starting as early as six months, across all time points, the treatment showed highly statistically significant changes in CDR-SB from baseline compared to placebo (all p-values are less than 0.01). All key secondary endpoints were also met with highly statistically significant results compared with placebo (p<0.01). Key secondary endpoints were the change from baseline at 18 months compared with placebo of treatment in amyloid levels in the brain measured by amyloid positron emission tomography (PET), the AD Assessment Scale-cognitive subscale14 (ADAS-cog14), AD Composite Score (ADCOMS) and the AD Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).

The incidence of amyloid-related imaging abnormalities-edema/effusion (ARIA-E), an adverse event associated with anti-amyloid antibodies, was 12.5% in the lecanemab group and 1.7% in the placebo group. The incidence of symptomatic ARIA-E was 2.8% in the lecanemab group and 0.0% in the placebo group. The ARIA-H (ARIA cerebral microhemorrhages, cerebral macrohaemorrhages, and superficial siderosis) rate was 17.0% in the lecanemab group and 8.7% in the placebo group. The incidence of symptomatic ARIA-H was 0.7% in the lecanemab group and 0.2% in the placebo group. There was no imbalance in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) between lecanemab (8.8%) and placebo (7.6%). The total incidence of ARIA (ARIA-E and/or ARIA-H) was 21.3% in the lecanemab group and 9.3% in the placebo group. Overall, lecanemab's ARIA incidence profile was within expectations.

Lecanemab is supplied for intravenous (IV) administration as a preservative-free, sterile, clear to opalescent, and colorless to pale yellow solution in a glass vial with an elastomeric closure. Lecanemab is supplied in single dose vials containing 500 mg/5mL or 200 mg/2 mL. Each mL of solution contains 100 mg of lecanemab and histidine (0.18 mg), histidine hydrochloride monohydrate (4.99 mg), arginine hydrochloride (42.13 mg), polysorbate 80 (0.50 mg), and water for Injection at an approximate pH of 5.0.

27. **Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?**

The use of a non-branded terms Aβ PET or CSF AD biomarker testing are not trademarked.

Lecanemab does not currently have a trade name and is undergoing TGA approval in Australia.

28. **If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?**

Not applicable

29. **If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e., accessibility, dosage, quantity, duration or frequency)?**

Test frequency

The intention is that a positive Aβ PET or CSF AD biomarker profile would be used for the confirmation of patient eligibility for initiation of treatment with lecanemab on the PBS. In a situation where the specialist assessments are inconclusive, a FDG PET will be performed. This assessment may indicate severe AD, or cognitive impairment due to causes other than AD. If the test is inconclusive testing will be repeated every 18 months.

Accessibility

CSF AD biomarker assay has been proposed as a secondary diagnostic for lecanemab eligibility, should any access issue to Aβ PET be identified, as the lumbar puncture procedure can be performed to collect CSF specimens for in vitro testing.

30. **If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:**

Medical services that may be required concurrently with Aβ PET

- Administration of the amyloid radiotracer is assumed to be part of the Aβ PET service.

Medical services that may be required concurrently with CSF Biomarker testing

- CSF sample collection would require a lumbar puncture (MBS item 39000) with or without anaesthesia, as required (MBS item 21945).

31. **If applicable, advise which health professionals will primarily deliver the proposed service:**

Aβ PET examinations should only be performed by, or under the supervision of, a registered nuclear medicine specialist. Specialists who interpret Aβ PET results should also complete appropriate training programs provided by the manufacturers of radiotracers.

A certified pathologist is usually primarily responsible for overseeing the CSF AD biomarker testing and reporting of results. It is proposed that CSF AD biomarker service could be undertaken at any NATA accredited pathology laboratory provided the laboratory's validation of the assay method had also been NATA accredited.

It is proposed that referral for Aβ PET and ordering of CSF AD biomarker tests be restricted to specialist clinicians (geriatricians, psycho-geriatricians, neurologists, and psychiatrists) involved in the diagnosis and care of patients with MCI or dementia.

32. **If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:**

PET services are not delegated or referred. PET services involve nuclear medicine specialists who consult with the patient, determine the relevant dosage and nature of the scan, review the available relevant clinical data and preparation of the report of the scan. The equipment is operated by trained technologists under the direction of the nuclear medicine specialist. Quality is assured by the nuclear medicine specialists. Other staff involved in the delivery of the service may include nurses and administration staff.

It is anticipated that a NATA accredited laboratory, overseen by a certified pathologist, would deliver a CSF AD biomarker testing service. Only appropriately qualified laboratory staff actually run the test procedures on behalf of the certified pathologist.

33. **If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:**

It is proposed that referral for Aβ PET and ordering of CSF biomarker tests be restricted to specialist clinicians (geriatricians, psycho-geriatricians, neurologists, and psychiatrists) involved in the diagnosis and care of patients with MCI or dementia.

34. **If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:**

Nuclear medicine specialists in Australia reading amyloid PET scans undergo accreditation. It is debated by experts as to whether this should be mandatory.

Training modules for all 3 tracers available online. Aβ PET services for patients with early-stage AD must be performed by:

a) a nuclear medicine specialist or consultant physician credentialed under the Joint Nuclear Medicine Specialist Credentialing Program for the Recognition of the Credentials of Nuclear Medicine Specialists for Positron Emission Tomography overseen by the Joint Nuclear Medicine Credentialing and Accreditation Committee of the Royal Australasian College of Physicians (RACP) and Royal Australian and New Zealand College of Radiologists (RANZCR);

or b) a practitioner who is a Fellow of either RACP or RANZCR, and who, prior to 1 November 2011, reported 400 or more studies forming part of PET services for which a Medicare benefit was payable, and who holds a current licence from the relevant State radiation licensing body to prescribe and administer the intended PET radiopharmaceuticals to humans. Furthermore, the product information for the radioactive tracers used in Aβ PET state that the images should be interpreted only by readers who have successfully completed training provided by the manufacturer of the tracer being used. 18F-flutafuranol (NAV4694) reader training can be provided by Austin Health, the Australian Dementia Network and the ANZ Society of Nuclear Medicine.

CSF AD biomarker testing

It would be expected, that consistent with other in vitro diagnostic assay kits for targeted therapies, that pathologist training and a quality assurance program would be developed.

It is also expected that each laboratory performing the test would need to establish its own reference ranges and validated cut-off values and NATA accreditation would be required.

35. **(a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):**

- ☒ Inpatient private hospital (admitted patient)
- ☒ Inpatient public hospital (admitted patient)
- ☒ Private outpatient clinic
- ☒ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☒ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☒ Private day surgery clinic (admitted patient)
- ☒ Private day surgery clinic (non-admitted patient)
- ☒ Public day surgery clinic (admitted patient)
- ☒ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Aβ PET services may be provided in both an inpatient and outpatient setting. CSF AD biomarker testing would be undertaken in a laboratory setting, but specimen collection and some pre-analytical handling of the specimen could take place in multiple admitted and non-admitted patient settings

36. **Is the proposed medical service intended to be entirely rendered in Australia?**

- ☒ Yes
- ☐ No

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

37. **Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the <u>Australian health care system</u>). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):**

There is currently no single test to identify AD. The diagnosis is made only after careful clinical consultation. Testing to detect amyloid pathology is not funded by the Commonwealth for patients with AD.

Therefore, the nominated comparator is "No testing for amyloid and therefore standard of care (SoC)".

There are currently no disease modifying treatments (DMTs) available for treating AD. Current treatments are for symptomatic relief only, as shown in Table 3. The SoC for patients with a clinical diagnosis of mild AD would be treatment with acetylcholinesterase inhibitor (AChEI) therapy as first line AD medication.

As per application 1643, the comparison is: "Testing for amyloid and where the test is positive, use of lecanemab + SoC " vs "No testing for amyloid and therefore SoC".

38. **Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?**

☐ Yes (please list all relevant MBS item numbers below)
☒ No

Not applicable

39. **(a) Will the proposed medical service/technology be used in addition to, or instead of, the nominated comparator(s)?**

☒ In addition to (i.e., it is an add-on service)
☐ Instead of (i.e., it is a replacement or alternative)

(b) If yes, please outline the extent to which the current service/comparator is expected to be substituted

### PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)

40. **Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e., the landscape <u>before</u> the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current <u>clinical management pathway</u>), but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g., pharmaceuticals, diagnostics and investigative services, etc.).**

In the current clinical pathway, a patient generally presents to their GP/physician with concerns regarding memory and/or cognition. The GP will conduct an investigation will include, patient history, cognitive assessments, medication review, blood tests, structural imaging. The GP will then refer the patient to a specialist, commonly a geriatrician, neurologist, psycho-geriatrician, or a psychiatrist.

The specialist will perform a number of specialist assessments which may inform a clinical diagnosis of AD, or be inconclusive. If the diagnosis is MCI possibly due to AD/prodromal AD, the patient will be monitored. If the assessment confirms mild AD, patients will then be treated with AChEI. If the diagnosis is moderately severe AD, the patient will be treated with AChEI or NMDA RA dependent on the severity of disease. If the diagnosis is severe, best supportive care will be provided.

In a situation where the specialist assessments are inconclusive, a FDG PET will be performed. This assessment may indicate severe AD, or cognitive impairment due to causes other than AD. If the test is inconclusive testing will be repeated every 18 months.
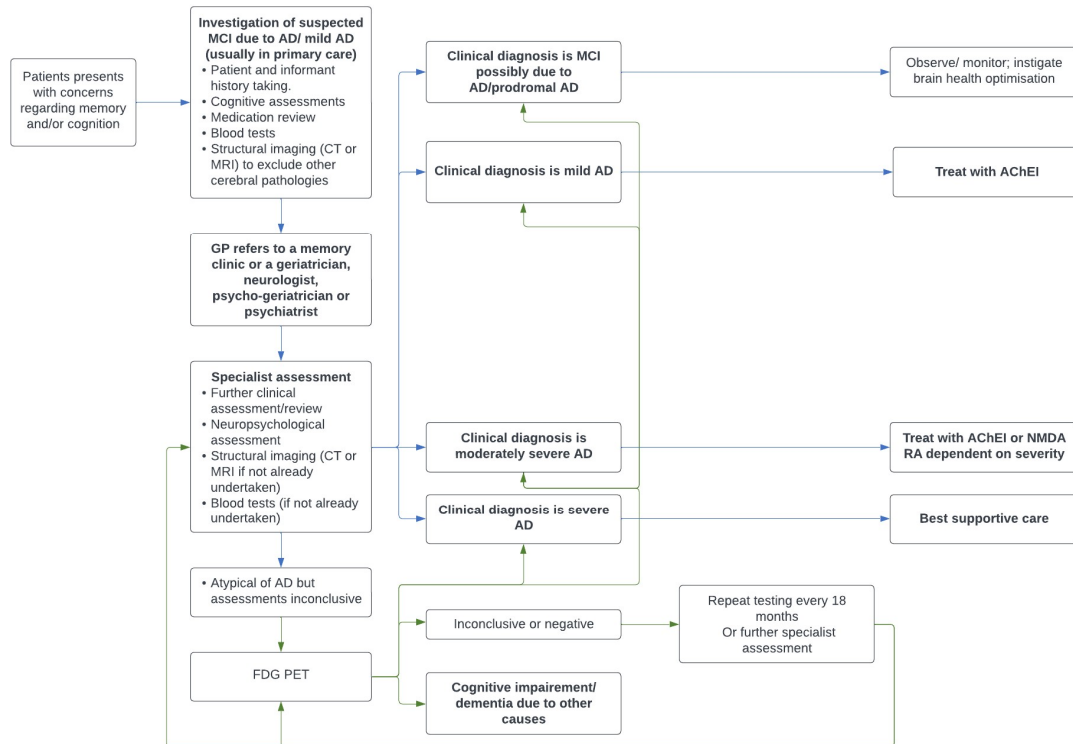
41. **Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow <u>after</u> the proposed service/technology is introduced, including variation in health care resources.**

In current Australian practice, there is currently no single test to identify AD. The diagnosis is made only after careful clinical consultation. Testing to detect amyloid pathology is not funded by the Commonwealth for patients with AD. Patients with a clinical diagnosis of MCI possibly due to AD are currently observed initially. There are currently no disease modifying treatments (DMTs) available for treating AD. Current treatments are for symptomatic relief only. Patients with a clinical diagnosis of mild AD generally receive an AChEI therapy as a first line AD medication. AChEI therapy is PBS subsided for patients with mild to moderately severe AD. It is proposed that the testing to detect AD/amyloid pathology be conducted sequentially upon receiving a clinical diagnosis and before any treatment with AChEI therapy. This ensures the optimal number of patients tested at the lowest cost to the Medicare system as the correct medication may help slow the progression of the disease.

In the proposed clinical pathway, all key events remain the same as the current clinical pathway up until the clinical diagnosis of AD. At this point, patients with MCI possibly due to AD/prodromal AD, and patients with a clinical diagnosis of mild AD will undergo a Amyloid PET. If the results of the Amyloid PET are positive, both cohorts of patients will be treated with lecanemab and SOC. If the results of the Amyloid PET are negative, both cohorts of patients will undergo a FDG PET, and then further investigation to identify an alternative likely cause of cognitive impairment. Treatment for moderately severe, and severe AD remains unchanged as clinical trials for lecanemab did not include this patient population. Patients found to be brain amyloid negative would still be eligible to AChEI therapy (standard of care, regardless of test result), according to the PBS restriction. Patients who subsequently progress to moderately severe AD may go on to receive a-methyl-D-aspartate receptor antagonist (NDMA RA) therapy.
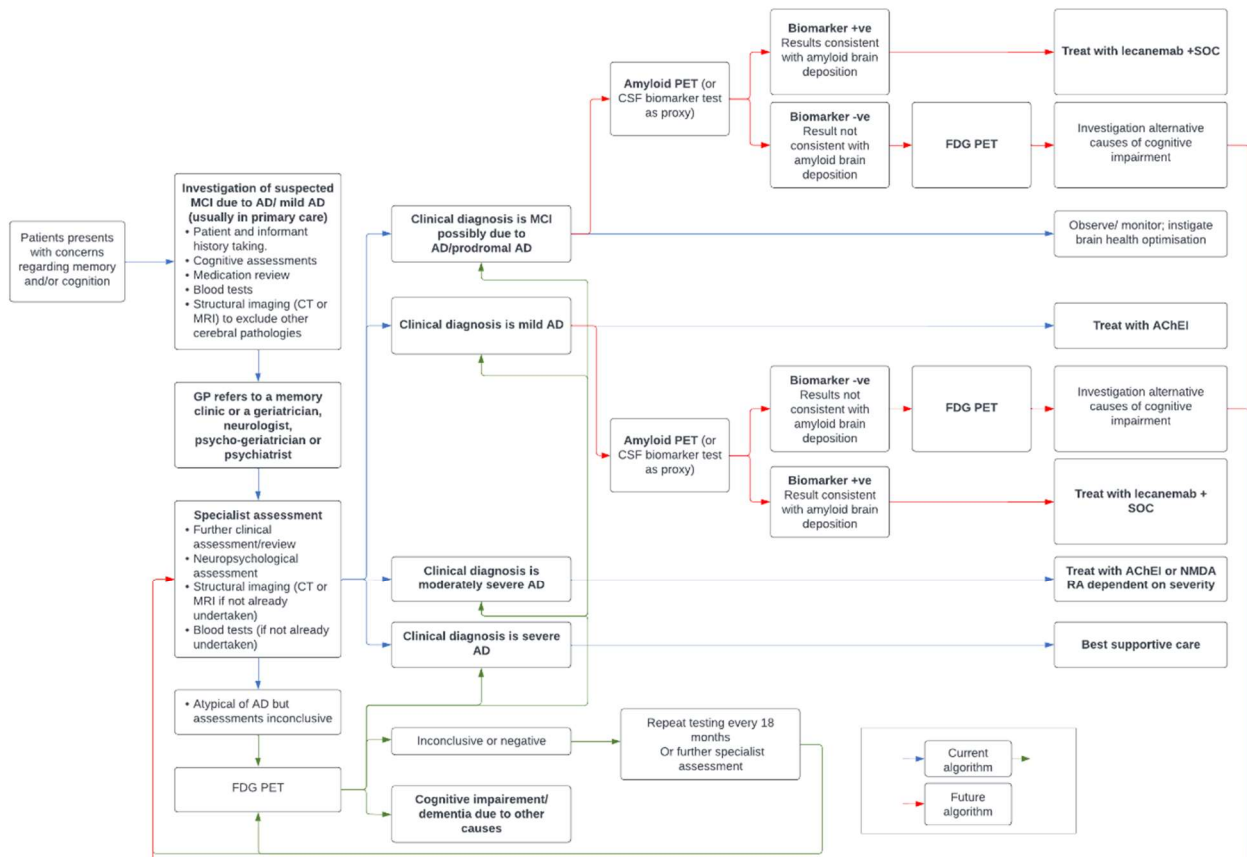
PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES

42. **Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):**

The proposed codependent technologies of the protein biomarker tests Aß positron emission tomography (PET) and cerebrospinal fluid (CSF) will provide access to a new Pharmaceutical Benefits Schedule subsidised lecanemab in patients with early-stage Alzheimer Disease. [31]

Historically, management of AD has aligned with guideline recommendations for clinical diagnosis based on symptoms, and treatment of cognitive, behavioural, and functional symptoms of AD only. The current treatment algorithm as outlined by guidelines is based on AChEI and memantine for mild, moderate, and severe AD dementia. These drugs provide only symptomatic relief, temporarily alleviating cognitive impairment, but do not treat the underlying cause of AD nor cure or halt the progression of the disease.[32][33] No symptomatic therapies are indicated for the treatment of MCI. Due to the high epidemiologic, humanistic, and economic burden of AD, there is an unmet need for disease modifying therapies (DMTs) that have been approved on the basis of efficacy in delaying the clinical progression of this disease.

Lecanemab binds with highest affinity to large soluble Aβ aggregates while maintaining high affinity for fibrillar Aβ that are a major component of Aβ plaques. The accumulation of Aβ plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Lecanemab reduces Aβ plaques and reduces downstream tau, as evaluated in its clinical trials.[34] A therapy that could delay or prevent the onset or progression of AD could improve patient HRQoL and reduce the considerable societal and direct cost burden associated with advanced stages of this disease.[35]

Lecanemab is indicated for the treatment of early AD (MCI due to AD and mild AD dementia, with confirmed amyloid pathology), the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease.

The clinical trial program for lecanemab for the treatment of adults with early AD includes two phase 1 trials, one 18-month phase 2 trial with extension, and one 18-month phase 3 trial with extension.[36] The primary endpoints in the phase 2 and phase 3 trials included change in ADCOMS and Clinical Dementia Rating – Sum of Boxes (CDR-SB) scores from baseline, respectively.[37][38]

During the phase 2 trial, treatment with lecanemab was associated with a dose- and time-dependent reduction in amyloid as assessed by positron emission tomography (PET) standard uptake-value ratio (SUVr). Amyloid positron emission tomography (PET) imaging allows in vivo assessment of cerebral amyloid load and can be used in the evaluation of progression of AD. However, cortical amyloid deposition can occur in healthy cases, as well as in patients with AD and quantification of cortical amyloid burden can improve the PET imaging evaluations. The quantification is mostly performed by cortical-to-cerebellum standardized uptake value ratio (SUVr). Each of the 5 lecanemab dose groups demonstrated significant reductions in amyloid (as measured by PET-SUVr) versus placebo (P<0.001 for all doses), with higher doses of lecanemab associated with greater reductions than lower doses.

Lecanemab treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months by 27%, which represents a treatment difference in the score change of -0.45 (p=0.00005) in the analysis of Intent-to-treat (ITT) population. Starting as early as six months, across all time points, the treatment showed highly statistically significant changes in CDR-SB from baseline compared to placebo (all p-values are less than 0.01). All key secondary endpoints were also met with highly statistically significant results compared with placebo (p<0.01). Key secondary endpoints were the change from baseline at 18 months compared with placebo of treatment in amyloid levels in the brain measured by amyloid positron emission tomography (PET), the AD Assessment Scale-cognitive subscale14 (ADAS-cog14), AD Composite Score (ADCOMS) and the AD Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL). Lecanemab was generally well-tolerated in the phase 2 trial, with comparable rates of treatment emergent adverse events (AEs) and serious adverse events (SAEs) across different dose and placebo groups. AEs leading to discontinuation, infusion related reactions, and ARIA-E (all ARIA-E events led to discontinuation per the protocol) were more frequent among patients who received lecanemab. Infusion reactions were mostly mild to moderate, and the incidence for the 10 mg/kg biweekly dosage group was 19.9%. The incidence of ARIA-E was <10% in the highest doses for the overall population, 9.9% in the 10 mg/kg biweekly dosage group, and 14.3% for participants that were ApoE4 positive. The incidence of amyloid-related imaging abnormalities-oedema/effusion (ARIA-E), an adverse event associated with anti-amyloid antibodies, was 12.5% in the lecanemab group and 1.7% in the placebo group. The incidence of symptomatic ARIA-E was 2.8% in the lecanemab group and 0.0% in the placebo group. The ARIA-H (ARIA cerebral microhemorrhages, cerebral macrohaemorrhages, and superficial siderosis) rate was 17.0% in the lecanemab group and 8.7% in the placebo group. The incidence of symptomatic ARIA-H was 0.7% in the lecanemab group and 0.2% in the placebo group. There was no imbalance in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) between lecanemab (8.8%) and placebo (7.6%). The total incidence of ARIA (ARIA-E and/or ARIA-H) was 21.3% in the lecanemab group and 9.3% in the placebo group. Overall, the lecanemab ARIA incidence profile was within expectations. The majority (60%) of cases of ARIA-E were mild to moderate, occurring in the first 3 months, and every case of ARIA-E resolved (mostly within 4 to 12 weeks of onset); 5 (10.4%) of the total 48 cases were symptomatic. Of the participants in the lecanemab (all treatment arms) group, 65 (10.7%) experienced amyloid related imaging abnormalities – haemorrhage (ARIA-H; new cerebral microhemorrhages, cerebral macrohaemorrhages, and superficial siderosis) versus in 13 (5.3%) of participants in the placebo group.[39]

After an average 24 month gap period upon completion and analysis of the core trial, participants were enrolled in an extension trial, and began treatment with 10 mg/kg of lecanemab biweekly for up to 60 months, or until the drug became commercially available.[40] Results of the extension trial demonstrated early reduction in brain amyloid, as 43% of patients demonstrated a conversion to negative brain amyloid as early as 3 months, and over 80% of participants were converted by 12 months versus placebo.[41] Plasma Aβ42/40 ratio and pTau181 are putative blood biomarkers that are used to screen for tau pathology associated with AD. The concentration ratio of Aβ42 to Aβ40 (Aβ42/40 Ratio) can be considered to be superior to the concentration of Aβ42 alone when identifying patients with AD. The plasma Aβ42/40 ratio and pTau181 decreased in participants after the gap while on treatment with lecanemab during the extension trial. During the extension trial, the incidence of ARIA-E was <10%, and all cases were in ApoE4 positive participants.[42]Combined analysis of the core and OLE trials demonstrated that the incidence of

symptomatic ARIA-E was approximately 2%.[43] This has been confirmed in the Ph3 CLARITY AD study, with a symptomatic ARIA rate of 2.8% out of 1795 enrolled patients.

As mentioned earlier, the nominated comparator in is "No testing for amyloid and therefore SoC". The SoC for patients with a clinical diagnosis of MCI possibly due to AD is observation, with instigation of brain health optimisation (generally encouragement of physical activity, social engagement, maintenance of cognitive stimulation and good nutrition). The SoC for patients with a clinical diagnosis of mild AD would be a treatment with AChEI therapy as first line AD medication.

It is proposed that amyloid testing followed by lecanemab treatment (with or without SOC) is superior to no amyloid testing and current SoC for patients with early-stage AD.

The clinical claim is justified by:

1. Acceptable safety and analytical performance of AD biomarker testing (assessed by MSAC);
2. Superior efficacy with acceptable safety of lecanemab based treatment in brain amyloid positive patients relative to standard of care (without amyloid testing) (assessed by PBAC);
3. Clinical utility of the test plus drug combination (assessed be MSAC/PBAC).

43. **Please state what the overall clinical claim is:**

The overall clinical claim is that the proposed codependent technologies (the protein biomarker tests Aß positron emission tomography (PET) and cerebrospinal fluid (CSF)) for determining eligibility for access to Pharmaceutical Benefits Schedule subsidised lecanemab in patients with early-stage Alzheimer Disease are superior in terms of comparative effectiveness versus the main comparator (no testing and current standard of care) in patients with early AD.

This will be explored in more detail in the submission.

44. **List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):**

To be assessed by clinical trial data, test protocols, evidentiary standards and literature reviews

Safety Outcomes:	Adverse events related to Aβ PET and CSF AD biomarker testing
	Safety and tolerability of lecanemab treatment assessed by AEs, physical examinations, laboratory findings, and vital signs.
Clinical Effectiveness Outcomes	Treatment effect modification of lecanemab in patients in patients with early AD.
	In the clinical trials of lecanemab, the patients were specifically defined as having mild cognitive impairment (MCI) due to mild AD dementia.
	Lecanemab preferentially binds with highest affinity to large soluble Aβ protein aggregates, known as protofibrils, while maintaining high affinity for fibrillar Aβ that are a major component of Aβ plaques. The accumulation of Aβ plaques in the brain is a defining pathophysiological feature of AD. High dose lecanemab has been shown to reduce Aβ plaque burden on amyloid positron emission tomography (PET) and, concomitantly, slows AD clinical disease progression in patients diagnosed as having MCI due to AD or mild AD, with confirmed amyloid brain pathology.[44]
QOL outcomes	Change in patient management due to amyloid testing
	Quality of life and QALYs of patients and carers
	Lost productivity of patients and carers

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

45. **Estimate the prevalence and/or incidence of the condition in the proposed population:**

Early-stage AD, which is the target condition of this application includes two patient population subgroups: patients with mild AD and patients with MCI caused by AD. Upon clinical diagnosis of early-stage AD through cognitive and/or neuropsychological testing, and CT or MRI scans, amyloid-beta biomarker testing (Aβ PET scans or CSF) will be utilised to confirm the early-stage AD diagnosis, making the patients eligible for treatment with lecanemab. Both subgroups are included in the proposed indication population for lecanemab: 'Lecanemab is indicated for the treatment of early AD (MCI due to AD and mild AD dementia, with confirmed amyloid pathology)'.

These two population subgroups are considered to be relatively distinct phases within the currently accepted classification of the dementia and AD continuum. There is a large degree of similarity between these two populations with the differentiation of mild AD from MCI being the significant interference in the ability to function at work or in usual daily activities (which is AD).[45] As a result, epidemiological data is reported separately for the mild AD and MCI patient populations.

The application adheres to the literature-based approach and presents epidemiological estimates that separates the mild AD and MCI patient populations. However, it should be noted that the application considers there to be potential for overlap between the two patient population subgroups and as such it would not be appropriate to combine population estimates as this would not give accurate estimates of overall population numbers. Accordingly, the extent of overlap between the MCI and mild AD patient populations will be further investigated in the co-dependent submission.

The application presents a top-down approach for estimating the prevalence of mild AD and MCI patients in Australia (Table 4).

The prevalence of mild AD is based on the prevalence of dementia in Australia. Australia's dementia statistics are derived from a variety of sources including administrative data, survey data and epidemiological studies. As each data source has incomplete coverage of people with dementia, it is difficult to accurately report how many Australians are living with dementia. For the purposes of this application, the prevalence of dementia is obtained from the estimates made by Dementia Australia for 2022.[46] The 2022 Dementia Australia Prevalence Data for dementia was modelled by the National Centre for Social and Economic Modelling (NATSEM) from the University of Canberra. The team have used a standard demographic modelling approach, in which age-sex dementia prevalence rates are applied to age-sex population projection estimates. The proportion of patients with mild dementia (defined as having a Clinical Dementia Rating (CDR) of 1.0) was reported in the AIHW 2012 report based on the study by Barendregt (1998)[47].

Data regarding prevalence and incidence of MCI vary considerably and are influenced by the age of the study population, the population setting and methods used to operationalise criteria. A Dementia Collaborative Research Centre (DCRC) funder University of Melbourne project[48] reported a prevalence of approximately 9% in the Australian population in its sixties, based on a study conducted by Anstey (2013). However, it also reported that prevalence rates of MCI varied from 6% - 12% in another recent study applying uniform criteria to harmonised data from geographically diverse cohorts for people over 60 years of age. While these studies only report the prevalence of MCI in the older population (60+ years of age), they may be considered as approximate estimations of prevalence throughout the Australian population because MCI mainly affects the older population, with the incidence rates rising as the age increases. The number of MCI patients likely to develop dementia is taken from a population based longitudinal study (Lipnicki et al. 2017)[49].

An alternative method to determine the prevalence of MCI patients was based on the prevalence of amnesic MCI patients reported in Sachdev (2014)[50] defined as patients with a cognitive impairment in the memory domain. Amnesic MCI is used as a surrogate for MCI suspected to be due to AD. In the Sachdev (2014) study, the patient population were not identified as having dementia, i.e. they did not have a

clinical dementia rating (CDR) Global Score >= 1. The choice of the appropriate method to determine prevalence of MCI will be further investigated using an advisory-board and discussed in the submission.

Finally, the proportion of mild dementia and MCI patients with AD dementia subtype was assumed to be 76% and 75% respectively, based on Knopman (2016)[51], although it should be noted that this estimate is not widely reported in the literature and will be clarified in the submission.

The incidence of dementia was obtained from AIHW reported data based on a study by Welberry et al. 2020[52]. The incidence data is used to determine the prevalence of dementia in Australia over the next three years. (see Table 5)

When a clinical diagnosis of early-stage AD is made, and other causes of the MCI or mild dementia can be ruled out, this is the stage when patients would be considered eligible for proposed co-dependent test services.

The test services, namely Aß positron emission tomography (PET) and cerebrospinal fluid (CSF) are further discussed in Q48 and Q49.

It is important to note that the uptake of the proposed codependent test services is likely impact the uptake of Lecanemab. The current uptake rate of Alzheimer's treatments was obtained from a report published by the DUSC in 2016[53]. While the prevalent population of early-stage AD indicates the population eligible for treatment with Lecanemab, the actual number of early-stage AD patients being treated with Lecanemab is likely to be a subset of the population already receiving treatment for mild-moderate AD. This is because unlike existing PBS listed treatments for mild-moderate AD, Lecanemab requires an additional test (either AB PET or CSF) to confirm amyloid-beta pathology, which will reduce the patient pool due to potential limited availability of AB PET machines and lack of patient uptake of CSF. The DUSC (2016) report was also used to estimate patient adherence to treatment.

Table 4: Epidemiology data for mild AD and MCI associated with AD

Parameter	Value	Source
Mild AD population		
Estimated incidence of dementia in Australia	16.8 cases per 1000 person years for people aged 65 and over	Reported by AIHW based on Walberry et al. 2022
Estimated prevalence of dementia in Australia in 2022	487,500	Dementia Australia 2022 estimates
Proportion of dementia population with mild dementia	55%	Figure cited in AIHW 2012 dementia in Australia report, based on Barendregt & Bonneux (1998)
Proportion of mild dementia patients with suspected AD	76%	Knopman 2016
MCI population		
Method 1		
Estimated prevalence of patients with MCI in Australia (in patients over 60 years of age)	9% of the Australian population over the age of 60	Reported in the Physical Activity Guidelines for Older Australians with Mild Cognitive Impairment or Subjective Cognitive Decline – published by the University of Melbourne
Proportion of MCI patients likely to develop dementia	4.7%	Reported by the AIHW based on the study published by Lipnicki et al. in 2017.
Proportion of MCI patients with suspected AD	75%	Knopman 2016
Method 2		
Estimated incidence of dementia in Australia	16.8 cases per 1000 person years for people aged 65 and over	Reported by AIHW based on Walberry et al. 2022

Australian population over the age of 65 without dementia	Approximately 4,000,000	ABS data and dementia prevalence estimates reported by Dementia Australia for 2022
Proportion of the population with MCI	2%	Sachdev (2014), Table 3, based on aMCI dementia population as this is the criteria most consistent with a diagnosis of AD rather than other form of dementia
Proportion of MCI patients with suspected AD	75%	Knopman 2016
Uptake rate		
Uptake rate of PBS listed Alzheimer's treatments	44%	Calculated based on the following: Estimated AD patients treated with PBS listed treatments = 65,757 (*Source: DUSC 2016*) Proportion of AD treatments indicated for mild-moderate AD = 90% (*Source: DUSC 2016*). Estimated patients treated with PBS listed treatments for mild to moderate AD = *59,181* Estimated number of mild dementia patients suspected to have AD in Australia = 135,854 (*Source: calculated using the prevalence of dementia in Australia in 2015 and then applying the proportions of patients with mild dementia (55%) and patients with suspected AD (76%).*
Uptake rate of Aß positron emission tomography (PET) and cerebrospinal fluid (CSF)	TBC	**REDACTED**

46. **Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:**

It is anticipated that most patients would require one or other of the proposed medical services, i.e. the biomarker tests, only once to determine eligibility for initial treatment with Lecanemab.

Administration of Lecanemab via intravenous infusion is according to a dosing regimen of once in two weeks.[54]

The protocols of the clinical trials for lecanemab prespecified that MRI should be performed to monitor the incidence of amyloid-related imaging abnormalities (ARIA) early on in treatment for safety purposes.

Whether or not MRI monitoring will be necessary with the use of lecanemab in clinical practice will not be known until the TGA label for lecanemab is finalised.

Should MRI monitoring be indicated, the Applicant assumes such MRI scans will be performed using existing MBS item numbers. The budget impact of any MRI monitoring, should it be required, will be incorporated within the submission.

47. **How many years would the proposed medical service/technology be required for the patient?**

Once to assess eligibility for lecanemab.

Administration of lecanemab via intravenous infusion is according to a dosing regimen of bi-weekly.

48. **Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:**

Table 5 presents estimates for the first full year of listing, 2023. Uptake of Lecanemab has not been estimated for the application but will be presented in the co-dependent submission.

49. **Estimate the anticipated uptake of the proposed medical service/technology over the next three years, factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors), as well as provide commentary on risk of 'leakage' to populations not targeted by the service.**

Table 5 presents estimates for the first three years of listing, namely 2023 to 2025. Uptake of Lecanemab has not been estimated for the application but will be presented in the submission. Capacity constraints limiting access to dementia specialists for the administration of diagnostic testing has been taken into account. There are additional capacity constraints with regards to AD biomarker tests, particularly for Aβ PET, whereby availability of radio tracers, spare capacity of PET machines and capacity of nuclear medicine physicians to meet demand could limit the availability of testing. That being said, the application considers that the provision of two means of screening for amyloid positivity (Aβ PET and CSF) will be adequate to meet demand for testing.

However, lumbar puncture specimens for in vitro testing (remotely if necessary) can be performed widely and CSF specimens can be couriered to the NDDL testing facility for assay from any location within Australia. Issues concerning leakage of services attributable to AD biomarker testing or lecanemab are not anticipated to be an issue for these services. It should be noted, these numbers are considered indicative only because they do not necessarily capture the flow/progression/natural history of MCI/mild-AD which may mean some patients have been double counted in this cross-sectional prevalence-based approach.

Table 5: Estimated number of mild AD and MCI patients from 2023 - 2025

Row	Parameter	Value	2023	2024	2025	Source/calculation
A	Projected Australian population		26,418,221.56	26,769,583.91	27,125,619.38	ABS data
B	Projected Australian population over the age of 65	16.6% of the Australian population	4,385,424.78	4,497,290.10	4,611,355.29	16.6% *A
	Epidemiology of mild AD					
C	Mortality rate of dementia	38 deaths per 100,000				
D	Incidence of dementia in Australia (65+ age group)	16.8 per 1000	73,675.14	75,554.47	77,470.77	16.8%*B
E	Estimated prevalence of dementia in Australia	487,500	502,273.99	517,495.71	533,178.74	Dementia Australia 2022
F	Proportion of dementia population with mild dementia	55%	276,250.69	284,622.64	293,248.31	55%*E
G	Proportion of mild dementia patients with suspected AD	76%	209,950.53	216,313.21	222,868.71	76%*F
	Epidemiology of MCI (with suspected AD) *Method 1*					
H	Estimated prevalence of MCI in Patients over 60 years of age	9%	394,688.23	404,756.11	415,021.98	9%*B

I	Proportion of MCI patients likely to develop dementia	5%	18,550.35	19,023.54	19,506.03	5%*H
J	Proportion of MCI patients with suspected AD	75%	13,912.76	14,267.65	14,629.52	75%*I
Epidemiology of MCI (with suspected AD) *Method 2*						
K	Australian population over the age of 65 without dementia		3,883,150.79	3,979,794.39	4,078,176.56	B-E
L	Proportion of population with MCI	2%	77,663.02	79,595.89	81,563.53	2%*K
M	Proportion of MCI patients with suspected AD	75%	58,247.26	59,696.92	61,172.65	75%*L
Uptake of Lecanemab						
N	Uptake rate of PBS listed AD treatments	**REDACTED**				
O	Mild AD population likely to take AD treatments		**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
P	MCI population likely to take AD treatments (method 1)		**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Q	MCI population likely to take AD treatments (method 2)		**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
R	Uptake of Lecanemab	TBC				

PART 8 – COST INFORMATION

50. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

The cost of Aβ PET is guided by MBS item 61559 (FDG PET study of the brain, performed for the evaluation of refractory epilepsy which is being evaluated for surgery). This MBS fee was proposed in MSAC Application 1195 "F-18 Fluorodeoxyglucose Positron Emission Tomography (FDG PET) for the diagnosis of Alzheimer Disease". The current application proposes that the cost of the FDG radiotracer be supplemented for the cost of the Aβ PET radiotracer.

The majority of the costs associated with the AD biomarker test include the Aβ PET ligand, PET scan and Aβ PET interpretation.

Costs associated with CSF biomarker testing include lumbar puncture, already reimbursed on the MBS (item numbers 21945, 39000, 23010), day private hospital admission for the performance of lumbar puncture (includes costs of occasional use of CT guided procedure) and the CSF test assay.

Patients receiving lecanemab will accrue monitoring costs which are assumed to be the cost of five magnetic resonance imaging scans in the first year. This is based on the sponsor's assumption used in its economic model[55]. The cost of an MRI scan is the same as the MBS fee for the item codes associated with MRI scans of the head (e.g. MBS Item code 63551). Costs associated with biomarker testing and administration of lecanemab are summarised in Table 6.

Table 6: Costs associated with biomarker testing and lecanemab administration

Resource	Utilisation per patient	Unit cost	Reference
Biomarker tests			
Amyloid PET			
Proposed MBS fee for Aβ PET	1	TBD	Temporary unit cost: Based on MBS item 61559 ($918.00) but supplementing the cost of the Aβ tracer.
CSF biomarker test			
Lumbar puncture	1	$205.30	MBS items 21945, 39000 and 23010
Day Private Hospital Charge	1	$521.00	Assumption based on cost of Minor Medical Procedures ($788; NHCDC Round 24 Tier 2; 1013) excluding the pathology cost ($267; NHCDC Round 24; 3005)[56]
CSF test assay	1	$325.00	Price of test assay for AD screen of three proteins by the National Dementia Diagnostics Laboratory[57]
Lecanemab			
Intravenous infusion of immunomodulating agent	1	$99.50	MBS Item 14245
Cost of Lecanemab	1	**REDACTED**	
Monitoring costs (for the first year)		**REDACTED**	**REDACTED**

51. Specify how long the proposed medical service/technology typically takes to perform:

Aβ PET is comprised of an initial exam by a nuclear medicine specialist or radiologist followed by administered with the radiotracer which requires 45-90 mins for the tracer to equilibrate. The patient then undergoes the PET or PET/CT scans, which typically takes 20 minutes to perform depending on the

tracer used. Finally, a specialist will interpret the results, which involves comparing CT and PET scans simultaneously to ascertain Aβ positivity and usually requires 15 minutes to complete.

CSF biomarker testing is comprised of an initial lumbar puncture half day procedure typically performed in a day clinic. The CSF sample is transported to the laboratory where a report is compiled outlining the results found in testing, which usually takes 1 day. Lecanemab is administered to patients by intravenous infusion on a bi-weekly basis. The expected infusion time is approximately 1 hour.

52. **If public funding is sought through the <u>MBS</u>, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.**

<u>**TEST 1**</u>

Category 5 – Diagnostic Imaging Services

Proposed item descriptor: Beta-amyloid positron emission tomography (PET) study of the brain, with or without quantitative assessment, for the evaluation of a patient with a clinical diagnosis of early-stage Alzheimer's disease, requested by the specialist or consultant physician, to determine if the requirements relating to the amyloid status for access to lecanemab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

The patient considered for this service must also meet specific PBS eligibility criteria for treatment with lecanemab other than the criterion relating to amyloid status.

MBS Fee: $TBC   Benefit: 75% = $####   85% = $###

<u>**TEST 2**</u>

Category 6 – Pathology Services

Quantification, by immunoassay methodology of amyloid and tau proteins in cerebrospinal fluid from a patient with a clinical diagnosis of early-stage Alzheimer's disease, requested by the specialist or consultant physician, to determine if the requirements relating to the amyloid status for access to lecanemab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

The patient considered for this service must also meet specific PBS eligibility criteria for treatment with lecanemab other than the criterion relating to amyloid status.

MBS Fee: $TBC   Benefit: 75% = $####   85% = $###

Additional consideration for a specific MBS item for infusion of the co-dependent drug treatment

The Applicant also seeks advice on the requirement or otherwise for a separate MBS item number for the administration of lecanemab. Lecanemab is administered to patients by intravenous infusion on a bi-weekly basis.

The Applicant notes that there are already MBS items number for intravenous drug administration, although neither is entirely appropriate for the administration of lecanemab:

"IMMUNOMODULATING AGENT, administration of, by intravenous infusion for at least 2 hours duration,

payable once only on the same day and where the agent is provided under section 100 of the Pharmaceutical Benefits Scheme" (Item 14245).

"CYTOTOXIC CHEMOTHERAPY, administration of, either by intravenous push technique (directly into a vein, or a butterfly needle, or the side-arm of an infusion) or by intravenous infusion of not more than 1 hours duration - payable once only on the same day, not being a service associated with photodynamic therapy with verteporfin or for the administration of drugs used immediately prior to, or with microwave (UHF radio wave) cancer therapy alone" (Item 13915).

Additional consideration for a specific MBS item for magnetic resonance (MRI) monitoring of patients on the co-dependent drug treatment

The protocols of the clinical trials for lecanemab prespecified that MRI should be performed to monitor the incidence of amyloid-related imaging abnormalities (ARIA) early on in treatment for safety purposes.

Whether or not MRI monitoring will be necessary with the use of lecanemab in clinical practice will not be known until the TGA label for lecanemab is finalised.

Should MRI monitoring be indicated, the Applicant assumes such MRI scans will be performed using existing MBS item numbers. The budget impact of any MRI monitoring, should it be required, will be incorporated within the Applicant Developed Assessment Report (ADAR).

53. **If public funding is sought through an <u>alternative (non-MBS) funding arrangement</u>, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.**

Not applicable.

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