Australian Government

Department of Health

MSAC Application 1643

Two testing options for determining eligibility for access to Pharmaceutical Benefits Schedule subsidised aducanumab in patients with early stage Alzheimer Disease

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):
Corporation name: Biogen Australia Pty Ltd
ABN: 30095760115
Business trading name: Biogen Australia Pty Ltd

Primary contact name: REDACTED

Primary contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers
Business: **REDACTED**
Mobile: **REDACTED**
Email: **REDACTED**

2. (a) Are you a consultant acting on behalf of an Applicant?

☐ Yes
☐ No

REDACTED

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

REDACTED

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?

☐ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

Two testing options for determining eligibility for access to Pharmaceutical Benefits Schedule (PBS) subsidised aducanumab in patients with early stage Alzheimer Disease (AD)

This is a co-dependent application for the drug aducanumab (brand name yet to be confirmed) and diagnostic tests to determine patient eligibility for access to Pharmaceutical Benefits Schedule (PBS) subsidised drug treatment.

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, aducanumab 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. *In the clinical trials of aducanumab, the patients were more specifically defined as having mild cognitive impairment (MCI) due to AD/prodromal AD or mild AD dementia*[1]*. These diagnoses require evidence of AD related pathology, specifically amyloid or cerebrospinal fluid (CSF) evidence of brain beta-amyloid. As the proposed indication for aducanumab for consideration by the Therapeutic Goods Administration (TGA) is not yet finalised, the Applicant proposes that that the target patient population be referred to as "early stage AD" for the purposes of the PICO application form.*

High dose aducanumab has been shown to reduce beta-amyloid (Aβ) plaque burden on amyloid positron emission tomography (PET) and, concomitantly, slows AD disease progression in patients diagnosed as having MCI due to AD or mild AD, with confirmed amyloid brain pathology.

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.

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 (Knopman 2001; Beach 2012). 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 only 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 likely to be most beneficial.

Confirmation of amyloid brain deposition by Aβ PET was an inclusion criterion for patient entry into the pivotal clinical trials of aducanumab. In addition, the application also proposes CSF AD biomarker testing as an appropriate alternative to Aβ PET, given CSF AD biomarker testing is highly concordant with Aβ PET in determining amyloid status in the brain. The availability of CSF AD biomarker testing on the MBS in addition to Aβ PET would help address any potential access issues for patients in some regions with limited PET scanning facilities. CSF AD biomarker testing would also offer higher throughput capabilities compared with Aβ PET.

[1] Note on terminology: For the purpose of this document, the terms "prodromal AD" and "MCI due to AD" are considered as interchangeable, and used to define people who have the biomarkers for AD and a memory impairment but who do not yet have impairments in their activities of daily living sufficient to make a diagnosis of dementia. Patients may be triaged for AD biomarker testing if they meet National Institute on Aging and Alzheimer Association (NIA-AA) criteria for MCI which is considered possibly due to AD or mild AD, based on clinical diagnosis alone.

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 aducanumab. Aducanumab is administered to patients by intravenous infusion on a monthly basis. The expected infusion time is approximately 1 hour.

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

"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 EMERGE and ENGAGE clinical trials for aducanumab 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 aducanumab in clinical practice will not be known until the TGA label for aducanumab 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).

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 disease (AD) is an insidiously progressive neurodegenerative disorder that represents the most common form of dementia. MCI due to AD/prodromal AD is the earliest symptomatic phase prior to the onset of dementia in the AD severity continuum (Figure 1).

Accurate clinical diagnosis can be difficult in early stage AD. Aβ plaque deposition in the brain, associated with lowered CSF levels of Aβ, is considered a pathological hallmark of AD and implicated in the pathophysiologic process underlying early AD progression. As such, in early stage AD, abnormal Aβ levels can provide greater diagnostic certainty.

Aducanumab is a new disease modifying drug for patients with early stage AD who are confirmed positive for Aβ pathology. The drug binds to aggregated Aβ (both soluble oligomeric and fibrillar) thereby reducing plaque burden and slowing AD disease progression. The proposed assessments are therefore to identify suitable candidates for treatment with aducanumab by confirming the presence of underlying Aβ through demonstration of pathological alternations in Aβ levels.

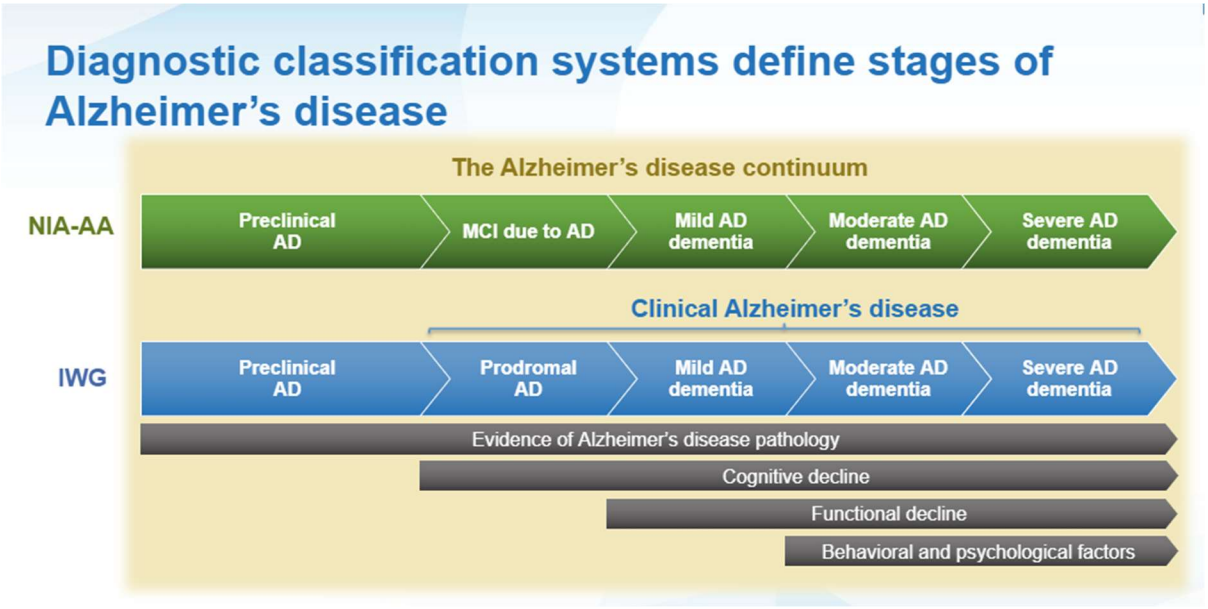

Figure 1 Stages of Alzheimer disease

AD, Alzheimer disease; MCI, mild cognitive impairment
Source: Albert 2011; Dubois, 2014; McKhann, 2011; Morris 2014; Sperling, 2011.

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 application requests consideration of two established and widely considered interchangeable methods for detecting presence of Aβ pathology in patients: Aβ PET and CSF AD protein biomarker testing (McKhann 2011; Jack 2018; Ossenkoppele 2015).

Aβ PET

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.

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.

CSF AD biomarker testing

CSF AD biomarker testing offers confirmation of the presence of Aβ and tau (including phospho-tau) brain pathology.

Numerous studies have evaluated the relationship between CSF AD biomarkers and Aβ PET and established there is strong inverse correlation between CSF levels of the amyloid and binding of Aβ PET tracers (Strozyk 2003). Measurement of the ratio of amyloid to another CSF AD biomarker, tau protein (which increases in AD) further improves the concordance between the Aβ PET and CSF test methods (Doecke 2020; Niemantsverdriet 2017; Janelidze 2017).

Testing for CSF AD biomarkers is therefore an appropriate alternative to Aβ PET to confirm Aβ pathology in order to determine eligibility for access to PBS subsidised aducanumab.

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 β-42 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.

As mentioned previously, the availability of CSF AD biomarker testing on the MBS in addition to Aβ PET would help address any inequity of access issues for patients in some regions with limited or no PET scanning facilities and also offer a high throughput capability.

Future developments

The Applicant is aware that blood-based assays for biomarkers of AD, including amyloid and tau proteins, are currently being researched. If developed for use in the clinical setting and validated against CSF and Aβ PET methodologies, blood-based assays for AD biomarkers could provide an alternative method for confirming the presence of amyloid brain pathology in the future (Khoury 2020).

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

☒ Yes
☐ No

i. **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)

New MBS items requested for Aβ PET and for CSF – Aβ, tau biomarker testing

This Medical Services Advisory Committee (MSAC) application is seeking new MBS item numbers for two proposed services, either of which would be used to determine the eligibility of a patient with a clinical diagnosis of early stage AD, for access to the co-dependent drug intervention, aducanumab, under the Pharmaceutical Benefits Scheme (PBS). There are no existing items on the MBS which could be used or amended to accommodate either of these services.

Additional consideration of requirement for an MBS item for infusion of the co-dependent drug treatment

The Applicant seeks advice on the requirement or otherwise for a separate MBS item number for the administration of aducanumab. As far as the Applicant is aware, there is no existing MBS item which would cover the administration of aducanumab. The Applicant notes that there are already MBS items number for intravenous drug administration (Item 14245; Item 13915), although neither is entirely appropriate to the administration of aducanumab.

ii. **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:**

Not applicable

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

Not applicable

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

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ 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)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

v. **Is the proposed service seeking public funding other than the MBS?**

No

8. What is the type of service:

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

The proposed services are intended to be used only in the context as a test to determine access to the co-dependent drug therapy, that is, only to be used in a well-defined patient population to confirm eligibility for a well-defined treatment (aducanumab) on the PBS. The rationale being that only patients with early stage AD with amyloidosis would be expected to derive therapeutic benefit from the proposed co-dependent drug aducanumab, which is a targeted therapy to Aβ. Confirmation of brain amyloid deposition by Aβ PET was an inclusion criterion for patient entry into the pivotal clinical trials of aducanumab.

Aβ PET or CSF biomarker testing provides an objective assessment to support a clinical diagnosis of AD with amyloid pathology underlying the patients' mild cognitive impairment or mild dementia. It is possible, and even likely, these tests will have at least some clinical utility outside of the decision to initiate treatment with aducanumab. However, for the purposes of the co-dependent assessment these benefits are likely to be described qualitatively rather than quantitatively and are not anticipated to be included in the assessment of the cost-effectiveness of the proposed testing strategy and treatment with aducanumab.

The Applicant is not proposing either of these services as standalone diagnostic services.

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

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

The co-dependent drug therapy, aducanumab, has been shown to be effective in reducing Aβ plaque burden and, concomitantly, slows AD disease progression in patients diagnosed as having early stage AD, with confirmed amyloid brain pathology.

The proposed services are intended to identify patients with amyloid brain pathology consistent with the patient population in whom the co-dependent drug, aducanumab, has been shown to be effective and therefore confirm the presence of the target considered to be central to the drug's mode of action. Confirmation of brain amyloid deposition by Aβ PET was an inclusion criterion for patient entry into the pivotal clinical trials of aducanumab.

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):

(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 time of lodgement of application form.
Generic name: Aducanumab

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):

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

☐ Yes
☐ No

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

☐ Yes
☐ No

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

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

<u>Key consumables for Aβ PET</u>
Radiopharmaceutical for Aβ PET imaging of the brain, for intravenous injection

<u>Key consumables for CSF Aβ and Tau assays</u>
Immunoassay kits and reagents

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Aβ PET radioactive tracers

Aβ PET imaging requires a radioisotope labelled tracer (or ligand) which specifically binds to amyloid plaque protein. A number of such ligands have been developed, of which the most well-known are: ^{11}C Pittsburgh B Compound (^{11}C-PiB); ^{18}F florbetapir; ^{18}F florbetaben, ^{18}F flutemetamol and ^{18}F flutafuranol (Table 1)

^{11}C Pittsburgh B Compound (^{11}C-PiB), a ^{11}C labelled thiamine T analogue (2-(4'-[^{11}C] methylaminophenyl)-6-hydroxybenzothiazole]), was developed as a research tool for investigating AD. ^{11}C-PiB was the first and remains the most studied Aβ PET ligand. In the research setting, ^{11}C-PiB is considered by some to be the gold standard Aβ PET tracer because it has a sufficiently high signal-to-noise ratio to quantify Aβ with PET imaging. However, ^{11}C-PiB has not been developed for commercial use, as the very short half-life of ^{11}C limits its use to imaging centres that have access to a cyclotron. Three ^{18}F labelled tracers for Aβ PET (^{18}F florbetapir; ^{18}F florbetaben; and ^{18}F flutemetamol) have been developed commercially and have received regulatory approval in jurisdictions outside of Australia (e.g., US and Europe). A fourth and newer ligand (^{18}F flutafuranol, also known as NAV4694) has higher binding to Aβ, is used in Australia for research and limited clinical use and is currently under development for wider commercial use.

There are currently no TGA registered radiotracers for Aβ PET. However, Aβ PET radiotracers are produced commercially in Australia by one company, Cyclotek. Cyclotek supplies PET radiopharmaceuticals for the Australian and New Zealand markets. The company has validated the manufacture of amyloid radiotracers, ^{18}F florbetaben (Neuraceq®) and ^{18}F flutemetamol (Vizamyl®) for intravenous injection, for use in Australia and New Zealand in the clinical trials setting and under Special Access Scheme (https://www.cyclotek.com/compounded-products/). Other producers of radiotracers for Aβ PET in Australia include a number of nuclear medicine departments of hospitals which have their own onsite cyclotrons. ^{18}F flutafuranol is produced by Austin Health Melbourne, Sir Charles Gardner Hospital Perth, Royal Brisbane Hospital, Liverpool Hospital Sydney and the South Australia Health and Medical Research Institute.

The Applicant understands that radiotracers for Aβ PET scanning do not currently require TGA approval under “extemporaneous compounding” exemption. However, ostensibly, this may be because their use is currently largely limited to research rather than mainstream clinical practice.

The Applicant notes that the TGA expects manufacturers of sterile radiopharmaceuticals to comply with the international Good Manufacturing Practice (GMP) standards, and a GMP license is required for commercial sale of radiotracers. Hospitals are generally exempt from this. As such, manufacturing standards across local producers of Aβ PET tracers may vary.

The Applicant is aware that there is a PET imaging service funded on the MBS where the PET ligand (^{68}Ga DOTA peptide used for PET study of gastroentero pancreatic neuroendocrine tumours - MBS Item 61647) is exempt from Australian Register of Therapeutic Goods (ARTG) listing requirement. Clarification is requested on whether exemption would also be considered for Aβ PET tracers.

Table 1 Radiolabelled ligands used in amyloid β PET scanning

Type of therapeutic good	Product details	Commercial availability	Brand name	Sponsor's name
Diagnostic radiopharmaceutical for PET	^{11}C [2-(4'-[11C] methylaminophenyl)-6-hydroxy-benzothiazole] ("^{11}C Pittsburgh compound B [PiB])	Not applicable	Not applicable	Not applicable
Diagnostic radiopharmaceutical for PET	^{18}F florbetapir for iv injection	Commercially available in some jurisdictions outside of Australia	Amyvid®	Eli Lilly
Diagnostic radiopharmaceutical for PET	^{18}F florbetaben for iv injection	Commercially available in some jurisdictions outside of Australia	Neuraceq®	PIRAMAL Imaging
Diagnostic radiopharmaceutical for PET	^{18}F flutemetamol for iv injection	Commercially available in some jurisdictions outside of Australia	Vizamyl®	GE Healthcare
Diagnostic radiopharmaceutical for PET	^{18}F flutafuranol for iv injection (NAV4694)	Widely available in Australia for research. Clinically available at Austin Health, Melbourne.	Not applicable	Cerveau Technologies have acquired licensing rights that cover Australia.

PET, positron emission tomography

Aβ and Tau CSF biomarker assay kits

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.

The Applicant understands that 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) (see: https://www.florey.edu.au/science-research/scientific-services-facilities/national-dementia-diagnostics-laboratory).

REDACTED

Table 2 Examples of CSF biomarker immunoassay kits that are commercially available outside of Australia

Type of therapeutic good	Product details	Brand name	Manufacturer/ Sponsor's name	Commercial availability
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 https://www.euroimmun.com/documents/Indications/Antigen-detection/Alzheimers-disease/EQ_6500_I_UK_A.pdf
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/docs/IGT_/80584.20090219.pdf
In vitro diagnostic test	Solid-phase enzyme immunoassay for the quantitative determination of AD biomarkers (amyloid and tau proteins) in human cerebrospinal fluid (CSF).	INNOTEST β-amyloid (1-42) INNOTEST phospho Tau (181P) INNOTEST hTAU Ag	Fujirebio/Asquith Diagnostics	Commercially available in some jurisdictions outside of Australia https://www.fujirebio.com/en/products-solutions/neurodegeneration

Type of therapeutic good	Product details	Brand name	Manufacturer/ Sponsor's name	Commercial availability
In vitro diagnostic test	ElectroChemiLuminescence 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 including Australia https://diagnostics.roche.com/global/en/products/params/elecsys-abeta42.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 https://www.fujirebio.com/en/products-solutions/neurodegeneration

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

15. (a) 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

Uncertain (as described above), but the base assumption is no.

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☒ Yes CSF AD Biomarker testing (if yes, please provide details below)

The Fujirebio INNOTEST CSF AD biomarker assays are TGA registered.

The Applicant understands also that the following Roche Diagnostics CSF AD biomarker testing kits were recently approved by the TGA (April 2020):

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

☒ No Aβ PET

No Aβ PET radiotracers have been listed or registered or included in the ARTG.

16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☐ Yes (please provide details below)
☒ No

As far as the Applicant is aware, no Aβ PET radiotracers are in the process of being considered for inclusion on the ARTG by the TGA.

17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the 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.

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 aducanumab and reimbursement submission for aducanumab.

PART 4 – SUMMARY OF EVIDENCE

18. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	**Title of journal article or research project**	**Short description of research****	**Website link**	**Date of publication*****
Available publications related to randomised controlled trials of aducanumab					
1.	Phase 1b randomised trial to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab	**Journal article entitled:** "The antibody aducanumab reduces Aβ plaques in Alzheimer disease" (Article includes interim results of the Phase 1b PRIME study) NCT01677572	Patients (N=165) with prodromal or mild AD, with brain Aβ pathology confirmed by Aβ PET scan, received placebo or aducanumab (1, 3, 6 or 10 mg/kg) monthly for one year. Dose and time dependent reductions in brain Aβ plaques and a dose-dependent slowing of clinical progression at one year were observed.	https://www.nature.com/articles/nature19323	31 Aug 2016

2.	Two Phase 3 randomised trials identically designed to validate the results of the PRIME Phase Ib trial, evaluating the safety and efficacy of aducanumab	**Conference presentation (Webcast and slide presentation) entitled:** EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer Disease Clinicaltrial.gov identifiers: NCT02477800 (ENGAGE) NCT02484547 (EMERGE)	Together the trials included 3,285 participants with MCI due to AD or mild AD with a positive Aβ PET scan who received monthly infusions of either high (10mg/kg) - or low (3, 6 mg/kg) -dose aducanumab or placebo. The intended treatment duration was 18 months. Key outcome measures were the change from baseline in: CDR-SB score (primary endpoint); MMSE; ADAS-Cog 13 and ADCS-ADL-MCI (secondary endpoints). Both trials were terminated following a negative futility analysis. However, pre-specified analyses of the intention to treat population showed that the high 10mg/kg dose group in EMERGE met its primary and secondary endpoints. Post-hoc analysis of the equivalent high 10mg/kg dose group in ENGAGE also met its clinical primary endpoint. In both EMERGE and ENGAGE, there was a dose and time dependent reduction of brain amyloid plaques.	**Webcast presentation** Register for free to access https://www.veracast.com/webcasts/clients/webcasts/v/0C1CC820A65F.cfm#/player/html5/speed/v150 **Slide presentation:** https://investors.biogen.com/static-files/ddd45672-9c7e-4c99-8a06-3b557697c06f **Biogen Press release** https://investors.biogen.com/news-releases/news-release-details/biogen-completes-submission-biologics-license-application-fda	These data were first presented on 5 Dec 2019 at the Clinical Trials on Alzheimer Disease (CTAD) Congress. The trial results are yet to be published in a peer reviewed journal.

	Type of study design*	Title of journal article or research project	Short description of research**	Website link	Date of publication***
Selected publications on the accuracy of Aβ PET versus post-mortem neuropathology for florbetapir, florbetaben and flutemetamol. (example publications; not a systematic search)					
3	Diagnostic accuracy	**Journal article entitled:** Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study	A prospective comparison of the sensitivity and specificity of amyloid PET imaging with neuropathology at autopsy. Amyloid assessed semiquantitatively with florbetapir PET was correlated with the post-mortem amyloid burden in the participants who had an autopsy within 2 years (Spearman ρ=0·76; p<0·0001) and within 12 months between imaging and autopsy (0·79; p<0·0001).	https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(12)70142-4/fulltext#%20	June 2012
4	Diagnostic accuracy	**Journal article entitled:** Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer disease: phase 3 study	Open-label, nonrandomized, multicenter, phase 3 study to validate the (18)F-labeled β-amyloid tracer florbetaben by comparing in vivo PET imaging with post-mortem histopathology. Florbetaben PET shows high sensitivity and specificity for the detection of histopathology-confirmed neuritic β-amyloid plaques (sensitivity 97.9% [95% confidence interval or CI 93.8-100%], specificity 88.9% [95% CI 77.0-100%]).	https://pubmed.ncbi.nlm.nih.gov/25824567/	March 2015

	Type of study design*	Title of journal article or research project	Short description of research**	Website link	Date of publication***
5		**Journal article entitled:** Performance of [18F]flutemetamol amyloid imaging against the neuritic plaque component of CERAD and the current (2012) NIA-AA recommendations for the neuropathologic diagnosis of Alzheimer disease	Determination of the accuracy of [18F]flutemetamol image read against Aβ at autopsy. High sensitivity and specificity to 3 neuropathologic criteria as Standards of Truth (SoT). Images are 100% specific when the SoT reflects both neuritic and diffuse plaques.	https://alz-journals.onlinelibrary.wiley.com/doi/abs/10.1016/j.dadm.2017.06.001	July 2017
Example publications on the concordance between Aβ PET radiotracers in determining the presence of amyloid brain pathology (example publications and derivation of cut-offs; not a systematic search)					
6	Concordance study	**Journal article entitled:** Amyloid PET imaging in Alzheimer disease: A comparison of three radiotracers	Study compared tracer retention for ^{11}C radiotracer Pittsburgh Compound B (PiB) with two ^{18}F amyloid radiotracers (florbetapir and flutemetamol) using two study populations. One group of subjects (N=40) underwent PiB and flutemetamol imaging sessions and a separate group (N=32) underwent PiB and florbetapir imaging sessions Cortical retention for each ^{18}F tracer was highly correlated with PiB, enabling conversion of thresholds across tracer measurement scales with a high level of internal consistency.	https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24647577/	20 March 2014

	Type of study design*	Title of journal article or research project	Short description of research**	Website link	Date of publication***
Example publications on the standardisation of quantitative amyloid PET using centiloid scaling methods (cut-offs; not a systematic search)					
7	Standardisation of amyloid PET	**Journal article entitled:** Standardized Expression of 18F-NAV4694 and 11C-PiB beta-Amyloid PET Results with the Centiloid Scale	Derivation of a scaling factor required to convert 18F-NAV4694 SUVRs to centiloids. The results for both 11C-PiB and 18F-NAV4694 can now be expressed in centiloids, an important step that should allow better clinical and research use of Aβ imaging	https://pubmed.ncbi.nlm.nih.gov/26912446/	Feb 2016
8	Standardisation of amyloid PET	**Journal article entitled:** 18F-Florbetaben PET beta-amyloid binding expressed in Centiloids	Derivation of linear equation required to convert FBB SUVRs to centiloid (CL) units. Relative performance of FBB and PiB in the same individuals using the standard CL methods. 18F-FBB binding is strongly correlated with PiB binding and FBB results can now be expressed in CL units	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5656696/	May 2017
9	Standardisation of amyloid PET	**Journal article entitled:** Standardization of amyloid quantitation with florbetapir standardized uptake value ratios to the Centiloid scale	Methods were applied to establish a conversion first from florbetapir SUVR values obtained using standard Centiloid VOIs to Centiloids and then from Avid (Joshi et al.) to Centiloids.	https://pubmed.ncbi.nlm.nih.gov/30006100/	July 2018

	Type of study design*	Title of journal article or research project	Short description of research**	Website link	Date of publication***
10	Standardisation of amyloid PET	**Journal article entitled:** Centiloid scaling for quantification of brain amyloid with [18F]flutemetamol using multiple processing methods	Application of the Centiloid scaling methods to images obtained using [18F]flutemetamol. [18F]flutemetamol has favourable performance compared with PiB and other β-amyloid tracers. Test-retest difference averaged 2%, with no difference between image processing pipelines.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6281542/pdf/13550_2018_Article_456.pdf	December 2018
Example publications on the concordance of CSF biomarker testing with Aβ PET in determining the presence of amyloid brain pathology (example publications and derivation of cut-offs; not a systematic search)					
11	Concordance study	**Journal article entitled:** Elecsys CSF biomarker immunoassays demonstrate concordance with amyloid-PET imaging	Retrospective analysis of a sub-cohort from the AIBL study of aging (Clinical diagnoses: CN [n=140]; MCI not necessarily due to AD [n=33]; AD [n=27] and FTP [n=2]) which utilised CSF samples and Aβ PET imaging data. Ratios Aβ42/Aβ40, tTau/Aβ42 and pTau/Aβ42 had higher ROC—AUC (all 0.94), and greater concordance with Aβ-PET (OPA ~ 90%), compared with individual biomarkers.	https://alzres.biomedcentral.com/articles/10.1186/s13195-020-00595-5	31 March 2020

	Type of study design*	Title of journal article or research project	Short description of research**	Website link	Date of publication***
12	Concordance study	**Journal article entitled:** Derivation of cut-offs for the Elecsys amyloid β (1–42) assay in Alzheimer disease	CSF collected from patients with mild-to-moderate Alzheimer disease were analysed by Elecsys immunoassays: (1) Aβ(1–42), (2) total tau, and (3) phosphorylated tau. Cut-offs (Aβ[1–42] and ratios with tau) were estimated by method comparison between AlzBio3 (n= 206), mixture modelling (n = 216), and concordance with florbetapir F 18 imaging-based classification (n = 75=). Based on three approaches, a 1100-pg/mL Elecsys® Aβ (1-42) cut-off is suitable for clinical trials with similar populations and preanalytical handling.	https://pubmed.ncbi.nlm.nih.gov/30426066/	2 August 2018
13	Concordance study	**Journal article entitled:** Alzheimer Disease Normative Cerebrospinal Fluid Biomarkers Validated in PET Amyloid-β Characterized Subjects from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study.	Aβ pathology was determined by PET imaging, utilizing ^{11}C-Pittsburgh Compound B, ^{18}F-flutemetamol, or ^{18}F-florbetapir, in 157 AIBL participants who also underwent CSF collection. Using an INNOTEST assay, cut-points were established (Aβ(1-42) >544 ng/L, T-tau <407 ng/L, and P-tau181P <78 ng/L) employing a rank based method to define a "positive" CSF in the sub-cohort of amyloid-PET negative healthy participants (n = 97), and compared with the presence of PET demonstrated AD pathology.	https://pubmed.ncbi.nlm.nih.gov/26401938/	May 2015

	Type of study design*	Title of journal article or research project	Short description of research**	Website link	Date of publication***
14	Concordance study	**Journal article entitled:** Agreement of amyloid PET and CSF biomarkers for Alzheimer disease on Lumipulse	The study cohort included participants diagnosed with either MCI (n = 35), AD dementia (n = 12), other dementias or neuro-degenerative diseases (n = 41), Controls were CN (n = 6). Aβ1-42, tTau and pTau (but not Aβ1-40) and the ratios with Aβ1-42 had good diagnostic agreement with ^{18}F-Florbetapir PET. The Aβ1-42/Aβ1-40 ratio had higher agreement and better correlation with Aβ PET than Aβ1-42 alone.	https://pubmed.ncbi.nlm.nih.gov/31464088/	2 August 2019

	Type of study design*	Title of journal article or research project	Short description of research**	Website link	Date of publication***
Selected publications on the concordance between CSF biomarker testing assay (example publications; not a systematic search)					
15	Concordance study	**Journal article entitled:** Concordance between cerebrospinal fluid biomarkers with Alzheimer Disease pathology between three independent assay platforms.	Prediction and concordance analyses were performed using a sub-cohort of 77 individuals (48 healthy controls, 15 with MCI, and 14 with AD) from the AIBL study of aging. The study confirmed strong concordance between CSF biomarkers and PET Aβ-amyloid status is independent of immunoassay platform. Concordance between dichotomised CSF biomarkers and PET Aβ-amyloid status was quite strong across all platforms.	https://pubmed.ncbi.nlm.nih.gov/29171991/	20 November 2017
16	Concordance study	**Journal article entitled:** Method Comparison Study of the Elecsys® β-Amyloid (1-42) CSF Assay Versus Comparator Assays and LC-MS/MS	Comparison studies evaluated the correlation between the Elecsys® β-Amyloid (1-42) CSF assay versus: INNOTEST® β-AMYLOID(1-42) (860 samples) and the Roche Diagnostics-developed LC-MS/MS method (250 samples); INNO-BIA AlzBio3 and the University of Pennsylvania (UPenn)-developed LC-MS/MS method (250 samples); and ADx-EUROIMMUN Beta-Amyloid (1-42) enzyme-linked immunosorbent assay (ELISA) (49 samples). Findings support use of the Elecsys® β-Amyloid (1-42) CSF assay to aid AD diagnosis. CSF-based certified reference materials should improve agreement across assays and mass spectrometry-based methods, which is essential to establish a global uniform CSF Aβ42 cut-off to detect amyloid pathology.	https://pubmed.ncbi.nlm.nih.gov/31129181/	23 May 2019

Aβ, amyloid beta; AD, Alzheimer disease; ADAS-Cog 13, Alzheimer Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version) AIBL, Australian Imaging, Biomarkers and Lifestyle Study of Ageing; AUC, area under the curve; CDR-SB, Clinical Dementia Rating sum of boxes; CERAD, Consortium to Establish a Registry for Alzheimer Disease; CI, confidence interval; CL, centiloid; CN, cognitively normal; CSF, cerebrospinal fluid; FBB, 18F florbetaben; FTP, frontotemporal dementia; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging and the. Alzheimer Association; OPA, overall percentage agreement; PET, positron emission tomography; PiB, Pittsburgh compound B; ROC, receiver operating characteristics; SoT, standard of truth; SUVR, standard uptake value ratios; VOIs, volumes of interest.

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*
***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*
**** If the publication is a follow-up to an initial publication, please advise.*

19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research	Short description of research **	Website link	Primary completion date according to clinicaltrials.gov record
1	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group	ENGAGE Study **Clinicaltrial.gov identifier:** NCT02477800 Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer Disease	Participants in the trial (N=1647) were with MCI due to AD or mild AD with a positive Aβ PET scan who received monthly infusions of either high-or low-dose aducanumab or placebo.	https://clinicaltrials.gov/ct2/show/NCT02477800?term=aducanumab&cond=Alzheimer+Disease&draw=2&rank=5	Trial has been terminated based on futility analysis **(see above: EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer Disease)**
2.	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group	EMERGE Study **Clinicaltrial.gov identifier:** NCT02484547 Study to Evaluate the Efficacy and Safety of Aducanumab (BIIB037) in Subjects With Early Alzheimer Disease	Participants in the trial (N=1638) were with MCI due to AD or mild AD with a positive Aβ PET scan who received monthly infusions of either high-or low-dose aducanumab or placebo.	https://clinicaltrials.gov/ct2/show/NCT02484547?term=aducanumab&cond=Alzheimer+Disease&draw=2&rank=4	Trial has been terminated based on futility analysis **(see above: EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer Disease)**

	Type of study design*	Title of research	Short description of research **	Website link	Primary completion date according to clinicaltrials.gov record
3.	A phase 3b single group assignment; open label clinical trial	EMBARK Study **Clinicaltrial.gov.identifier:** NCT04241068 A study to evaluate safety and tolerability of aducanumab in participants with Alzheimer disease Who had previously participated in the aducanumab studies 221AD103, 221AD301, 221AD302 and 221AD205	Participants in the trial (estimated n=2400) will be administered 10 mg/kg by iv infusion every four weeks for a total duration of 100 weeks. The primary endpoints comprise safety endpoints (AEs; SAEs; AEs leading to study and treatment discontinuations; ARIA-E and ARIA-H events) and presence of serum anti-aducanumab antibodies.	**https://clinicaltrials.gov/ct2/show/NCT04241068?term=aducanumab&cond=Alzheimer+Disease&draw=2&rank=1**	Currently enrolling by invitation Estimated primary completion date: Sept 2023

Aβ, amyloid beta; AD, Alzheimer disease; AE, adverse events; ARIA-E, amyloid-related imaging abnormalities suggestive of vasogenic oedema and sulcal effusions ; ARIA-H, amyloid-related imaging abnormalities - haemosiderin deposits; MCI, mild cognitive impairment; PET, positron emission tomography; SAE, serious adverse events.

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*
***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*
****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

The Australasian Association of Nuclear Medicine Specialists (AANMS)

(Letter of Support is provided with this application)

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

Not applicable

22. List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

Dementia Australia

(Letter of Support is provided with this application)

23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

Refer to Tables 1 and 2 (Response to Q15)

24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

REDACTED.

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. 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:

The condition targeted in this application is early stage symptomatic AD, which includes patients with MCI due to AD/prodromal AD or mild AD.

Dementia is an umbrella term for a set of symptoms including impaired memory and thinking. It is a term that is often associated with the cognitive decline of ageing. Dementia has numerous different underlying causes or disease.

Alzheimer disease (AD) is the most common cause of dementia, accounting for 50% to 70% of all cases (Rizzuto 2012; Winblad 2016). Alzheimer Disease International estimates that, as of 2018, there were about 50 million people living with dementia worldwide and that this figure may increase to 152 million by 2050 (Alzheimer Disease International 2018). While not a natural part of ageing, the prevalence of AD and other forms of dementia increases rapidly with age. According to 2011 data from the Australian Institute of Health and Welfare (AIHW), 9% of Australians aged 65 and over and 30% of Australians aged 85 and over had dementia (AIHW 2012).

In 2020, there is an estimated 459,000 persons living with dementia in Australia, with an annual growth rate of 3.8% in the prevalence of dementia for males and 2.5% for females. Without a medical breakthrough, the prevalence of dementia is projected to increase to 590,000 by 2028 and to over 1 million by 2058 (Dementia Australia 2018).

Dementia, including AD – as listed on death certificates – is now the second leading cause of death of Australians overall, and the leading cause of death in women; it is contributing to approximately 5% of all deaths in males and 11% of all deaths in females in 2017 (AIHW 2019). However, it has been estimated that deaths with dementia identified as the underlying cause of death on death certificates represent only 15% of all deaths in males with dementia and around 22% of all deaths in females with dementia (Brown 2017).

Clinically, AD is an incurable progressive neurodegenerative disorder characterised by an insidious and unrelenting decline in cognition and behavioural disturbances that result in the person's inability to perform usual activities of daily living (Jack 2013). Thus, AD patients develop increasing reliance on caregiving as the disease progresses, with partial or intermittent caregiving needs in the early stage of the disease and full-time care needs as the patient transitions to the severe stage of the disease. The economic and societal impact of AD is significant (Brown 2017).

Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing β-amyloid (Aβ) peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins.

The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome remain to be fully elucidated, but the leading hypothesis — the "amyloid cascade"— proposes that the driving force behind the disease process is the accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain (Hardy 2002). Evidence suggests the pathophysiological changes begin up to 20 years before clinical onset and as the disease progresses, cognitive impairments, behavioural changes, and functional disability manifest (Jack 2013).

The current view of AD, the disease process and its clinical manifestations, is that it manifests along a continuum (Figure 2) rather than having categorical stages. As such, there are no clearly identifiable fixed events that define its onset or the points at which an individual transitions from the asymptomatic phase (preclinical AD) to the symptomatic predementia phase (prodromal AD is also referred to as mild cognitive impairment (MCI) due to AD, and this is the stage where there are obvious symptoms of brain dysfunction)

(Sperling 2011), or from the symptomatic predementia phase to dementia onset (Mckhann 2011). *That said, cut-offs are sometimes applied when using some assessment scales used to rate the severity of cognitive impairment and dementia*.

Patho-physiologically, the development of amyloid plaques and neurofibrillary tangles occurs in a preclinical phase of disease. Over time the accumulation of plaques and tangles lead to synapse dysfunction and loss of neurons, at which point early signs of cognitive impairment become apparent.

There follows a phase of AD when individuals experience a gradually progressive cognitive decline that results from the accumulation of AD pathology in the brain. When the cognitive impairment is sufficiently great, such that there is interference with daily function, the patient is diagnosed with AD dementia, with dementia further subdivided into mild, moderate, and severe stages.

As AD progresses, gross atrophy occurs in specific brain regions, leading to more noticeable and progressive cognitive decline (Sperling 2011).

Clinical need

As mentioned earlier, there is currently no cure for AD. Existing medication therapies, such as acetylcholine esterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, are used to treat the cognitive symptoms of dementia. However, these drug therapies only provide a modest effect in the short-term (Birks 2006; Noetzli 2013) and limited or no benefit in the longer-term (DUSC 2016). As such, and given the increasing burden of AD, there is a great clinical need to develop drug therapies that target patients earlier on in the AD continuum, including prior to the onset of dementia, that act to modify the course of the disease. Potential disease-modifying drug candidates are currently under investigation. These candidates include small molecules and immunotherapy that target the Aβ pathway and aim to provide therapeutic benefit by reducing either soluble or insoluble forms of Aβ in the brain and cerebrospinal fluid (CSF). The proposed co-dependent drug in this application, aducanumab, is one such drug.

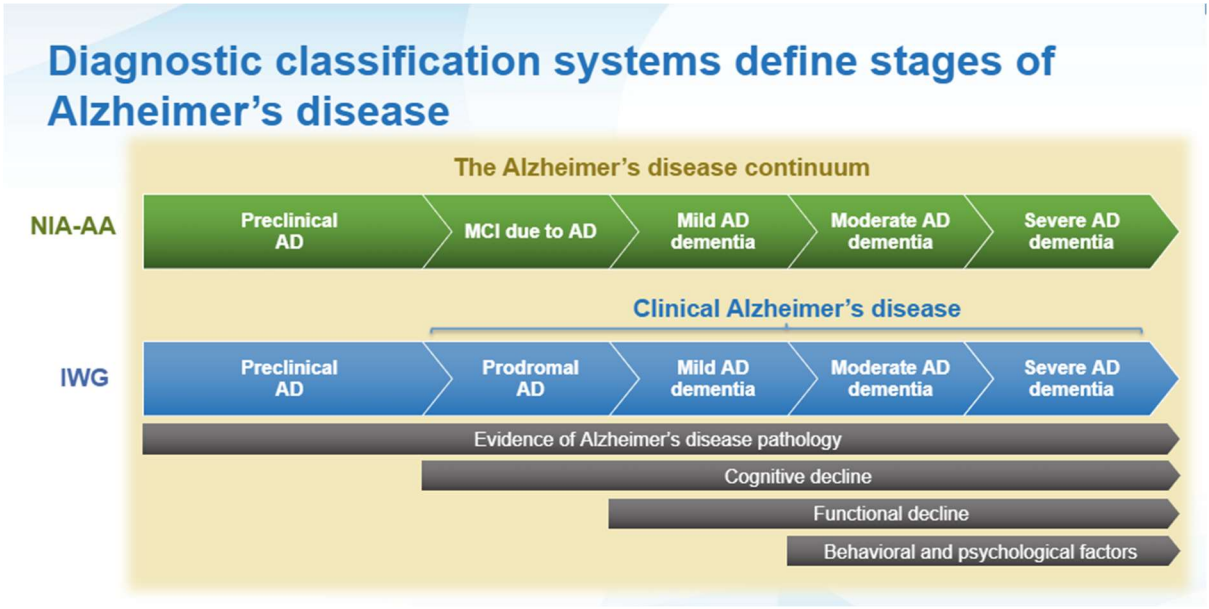

Figure 2 Alzheimer disease continuum.

AD, Alzheimer disease; IWG, International Working Group; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging and Alzheimer Association

Source: Albert 2011; Dubois 2014; McKhann 2011; Morris 2014; Sperling 2011.

26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

Characteristics of patients proposed eligible for the proposed medical services

Patients proposed as eligible for the proposed medical services are those meeting core clinical criteria for early stage AD (MCI or mild severity dementia), where, after ruling out other causes of cognitive impairment (e.g. vascular, traumatic, medical), and based on clinical assessments and evaluations, the diagnosing clinician judges the underlying cause to be AD, but where such a diagnosis has yet to be verified by Aβ biomarker evaluation. **In addition, to be eligible for the proposed medical services, patients would also have to meet specific PBS eligibility criteria (yet to be finalised[2]) for treatment with the co-dependent drug, aducanumab, other than the verification of the presence of amyloid brain pathology** (which would be determined by the proposed services), e.g., based on age and Mini Mental State Examination (MMSE) score restrictions.

While a diagnosis of early stage AD may be suggested by clinical assessment and evaluation alone, biomarker evidence of AD neuropathology provided by Aβ PET scanning or CSF analysis would provide additional support of AD as an underlying causal factor (a lack of neuritic amyloid plaques is inconsistent with a neuropathologic AD diagnosis) and the presence of brain amyloid deposition which is the aducanumab drug target.

No other patients are intended for the proposed services.

Early Stage AD

MCI due to AD / Prodromal AD

Based on the National Institute on Aging - Alzheimer Association (NIA-AA) guidelines (Albert 2011), the core clinical criteria for the diagnosis of MCI are as follows: a concern about changes in cognitive abilities; impairment in one or more cognitive domains greater than would be expected for the patient's age and educational background; preservation of independence in functional abilities – patients with MCI generally maintain their independence of function in daily life, with minimal aids or assistance; not demented— in as much that cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning.

AD dementia

According to the NIA-AA (McKhann 2011), the core clinical criteria for all-cause dementia are as follows: the presence of symptoms which interfere with the ability to function at work or at usual activities; an insidious onset and progressive cognitive decline; impairment in two or more cognitive domains (an amnestic presentation is most common, common, but the criteria allow for diagnosis based on non-amnestic presentations, e.g. impairment in executive function and visuospatial abilities); and the absence of prominent features associated with other dementing disorders.

AD may be suspected as the probable underlying cause of the dementia based on the presence of the following clinical features: the dementia has an insidious onset; there is a clear cut history of worsening of cognition; the initial and most prominent cognitive deficits are evident on history and examination in either amnestic presentation or non-amnestic presentation (language presentation, visuospatial presentation, executive dysfunction). Finally, there must be no evidence of other possible causes of dementia (e.g., substantial concomitant cerebrovascular disease, core features of Dementia with Lewy bodies other than dementia itself; prominent features of behavioural variant frontotemporal dementia; prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

[2] *Please note: The PBS clinical criteria are yet to be finalised but are anticipated to align closely with the key inclusion criteria of the pivotal clinical trials for the co-dependent drug aducanumab (see Section 6, Question 46* - Table 4).

Atypical course or etiologically mixed presentations which otherwise meet all the core clinical criteria for AD also may be considered possible AD dementia.

Severity of cognitive impairment or dementia

The severity of the cognitive impairment or dementia (e.g. as MCI or mild, moderate, or severe dementia) may be staged using widely accepted clinical global staging systems such as the Clinical Dementia Rating and/or cognitive test performance. However, the differentiation of MCI from mild dementia essentially rests on the determination of any significant interference in the ability to function at work or in usual daily activities. This is inherently a clinical judgment made by a skilled clinician through evaluation of the individual circumstances and the descriptions of daily affairs obtained from the patient and a knowledgeable informant.

How a patient would be investigated, managed, and referred within the Australian health care system in the lead up to being considered eligible for the service:

The following information is based on local practice guideline publications and web resources (Dyer 2016; Laver 2016; Dementia Pathways.com.au) and the advice of local clinical experts experienced in the diagnosis and management of patients with cognitive impairment.

The investigation, management, and referral pathway for patients in the lead up to being considered eligible for proposed service would essentially be consistent with the current pathway for specialist confirmation of diagnosis of MCI or dementia with clinical features consistent with AD as the underlying cause.

A patient's first presentation could be unanticipated or planned; that is, a patient may first present to the general practitioner (GP) during a standard consultation or because of the patient's self-reported or a family member's concern for their memory or cognition.

Over a number of consultations, the GP will undertake a comprehensive assessment of the patient, which includes a history taking from the patient and, if possible, a person who knows the patient well; cognitive and mental state examination with a validated instrument; and a physical examination.

Generally speaking, the clinical features of the early stage AD would require confirmation by a specialist.

As such, GPs would need to refer a patient to specialist service (e.g., memory clinics or the Cognitive, Dementia and Memory Service (CDAMS) in the state of Victoria) 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 disease), forwarding record of brief clinical history, investigation results, past history of drug lists and MMSE and/or other supporting assessments.

There are many assessment tools which might be used to aid diagnosis. Examples include: the Montreal Cognitive Assessment (MoCA); the Mini-Mental State Examination (MMSE); and the Alzheimer Disease Assessment Scale – Cognitive (ADAS Cog). There are also specific tools developed for the cognitive assessment of remote living Aboriginal and Torres Strait Islander populations and for people from non-English speaking backgrounds which are recommended for use where illiteracy language or cultural considerations deem their use appropriate.

Investigations to rule in or rule out causes of cognitive impairment other than AD may also be undertaken at this stage. These investigations generally will include blood tests (full blood count; urea and other electrolytes, liver function tests, calcium, thyroid function tests, serum vitamin B12 and folate) and possibly structural brain imaging (e.g. computerised tomography). The GP will also review the patient's existing medications to assess their possible effects on cognitive functioning and consider other causes (including comorbidities such as delirium or depression).

For the confirmation of diagnosis, the specialist would undertake further assessment of the patient's cognitive impairment. In addition, neuropsychological testing (which is not MBS funded) may be considered. Blood tests and structural imaging to exclude other cerebral pathologies would be undertaken at this stage if not undertaken previously. In some cases, where a diagnosis is equivocal, the patient may additionally undergo functional imaging with single proton emission computerised tomography [SPECT], which is MBS funded, or with fluorodeoxyglucose positron emission tomography (FDG-PET), which is not MBS funded and consequently not widely available.

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

Patients diagnosed with moderate or severe AD would not be eligible for the proposed services because they would not meet the anticipated eligibility criteria for treatment with co-dependent drug (aducanumab) on the PBS (which would be consistent with the inclusion criteria for patients who enrolled in the clinical trials for aducanumab). This is likely to mean that patients with MMSE score less than 20 or Clinical Dementia Rating global score of 2 or 3 would not be eligible for the proposed services.

Currently, in the absence of the proposed test services, onward treatment would be dependent on the severity of AD. There is currently no medication therapy approved for the treatment of MCI due to AD. These patients would be encouraged to optimise their brain health through physical activity and good nutrition, and return for reassessment after a period of 6-18 months. Patients diagnosed with mild to moderately severe AD may be considered for medication therapy (an acetyl choline esterase inhibitor (AChEI) therapy e.g. donepezil or and N-methyl-D-aspartate receptor antagonist (NDMA RA) therapy e.g., memantine, dependent on MMSE score). Patients diagnosed with severe AD would receive supportive care only.

27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

The clinical management pathway **before** patients would be eligible for the proposed medical services has previously been described in the answer to Question 26. A patient would be considered eligible for the proposed co-dependent tests at the point at which a specialist makes a clinical diagnosis of early stage Alzheimer Disease.

A flow chart depicting the current clinical management pathway up to this point is provided in Attachments.

REDACTED

PART 6b – INFORMATION ABOUT THE INTERVENTION

28. Describe the key components and clinical steps involved in delivering the proposed medical service:

Aβ PET

Delivery of Aβ PET scanning can be broken down into 4 key "phases". These are: (1) ^{18}F-tracer preparation and administration; (2) image acquisition; (3) image reconstruction and interpretation; and (4) documentation and reporting.

Radiotracer preparation and administration

It is anticipated that ^{18}F radiotracers will be either sourced from a commercial supplier or prepared in-house in facilities with a cyclotron and radio-pharmacy capability.

The ^{18}F 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 ^{18}F 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. The characteristics of radiotracers (^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben) which are currently commercially available outside of Australia and the investigational tracer ^{18}F-flutafuranol (NAV4694) widely used in Australia are outlined in Table 3.

Note: the proposed service for Aβ PET can utilise any available radiotracer and does not specify use of any one particular Aβ PET radiotracer.

Table 3 ***Recommended dose, dose volume, dose time, waiting period and acquisition duration for 18-F radiotracers used for Aβ PET***

Radiotracer	Dose	Dosing volume	Wait (min)	Acquisition time (min)	Absorbed radiation in an adult (mSv)
^{18}F-florbetapir	370 MBq (10 mCi)	Max 10 mL single iv bolus	30-50	10	7
^{18}F-flutemetamol	185 MBq (5 mCi)	Max 10 mL single iv bolus within 40 sec	60-120	10 -20	5.9
^{18}F-florbetaben	300 MBq (8 mCi)	Max 10 mL single iv bolus within 60 sec	45-130	15 - 20	5.8
^{18}F-flutafuranol (NAV4694)	200 MBq (6 mCi)	Max 10 mL single iv bolus	50	15 - 20	4.5

Sources: Minoshima 2016; US Product Information for ^{18}F-florbetapir, ^{18}F-flutemetamol and ^{18}F-florbetaben; Rowe 2016.

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. The recommended dose, waiting period, and acquisition duration are summarized in Table 3.

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, ^{18}F-florbetapir, ^{18}F-flutemetamol and ^{18}F-florbetaben tracers offer a reasonable compromise between radiation exposure following "as low as reasonably achievable (ALARA)" principles and image quality. The radiation exposure from an amyloid PET study—at about 4–7 mSv—is within the range of commonly performed imaging studies (Table 3).

The use of a computerised tomography (CT) scan to calculate attenuation correction for reconstruction (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 ± 1.3 mSv effective dose. The actual radiation dose is operator and scanner dependent. When CT is acquired at low dose only for attenuation correction, the dose is <0.5 mSv.

Equipment specification

Amyloid PET scans may be acquired on PET, PET/CT, or PET/ MR (magnetic resonance) systems from various manufacturers. The newest-generation scanners typically offer the best image resolution and differentiation of grey matter from white matter. For Aβ brain scans, a dedicated head holder is important

for positioning the head and limiting its motion. If a PET/CT or PET/MR system is not used, attenuation correction using an attenuation source or calculated attenuation correction must be used.

PET image reconstruction and interpretation:

It is important to note that the objective of the image interpretation is to estimate β-amyloid neuritic 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 assessment of tracer uptake in the grey matter.

Note: Visual interpretation, as described in the product information for each of the different radiotracers for amyloid PET, comprises a qualitative binary interpretation algorithm of a positive or negative scan. However, variability between tracers, PET scanners, procedural factors, and analysis methods across imaging centres are currently driving attempts for quantitative standardisation of amyloid PET (Amadoru 2020; Klunk 2015).

The Applicant suggests the proposed service should include quantification in standardised uptake value ratio (SUVR) or preferably centiloids. CSIRO provides this service via the Web. PET camera manufacturers can also be expected to provide this.

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.

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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.

Analysis – assay procedure

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 Fujirebio INNOTEST and the Roche Elecsys assays validated by the NDDL to generate pre-defined cut-offs for amyloid positivity and negativity. However, only the Elecsys and Lumipulse test kits provide pre-defined cut-offs for amyloid positivity and negativity.

Note: A proposed service for CSF AD biomarker testing can utilise any available CSF AD biomarker assay kit or platform.

Treatment with the co-dependent drug intervention - aducanumab

Patients fulfilling clinical criteria for early AD and subsequently found to be positive for brain amyloid, based on the co-dependency test result, would then be considered eligible for treatment with aducanumab.

Mechanism of action of aducanumab

Aducanumab is a unique human, anti-Aβ immunoglobulin (Ig) G1 monoclonal antibody that selectively binds to amyloid β fibrils and soluble oligomers. It targets and binds an epitope (small section of protein) in the aggregated form of Aβ which is not normally accessible in the Aβ monomer. Through this mode of action, aducanumab reduces the amount of Aβ, including the number of amyloid plaques, present in the brain. It is proposed that by reducing Aβ burden in the brain, including toxic species, aducanumab may slow neurodegeneration and reduce disease progression.

Treatment dosage and administration and intended course of treatment

It is proposed that aducanumab is administered via intravenous infusion once every 28 days. Aducanumab will be initiated at 1mg/kg and with dose escalation to 3mg/kg, 6mg/kg and 10mg/kg dose that is safely tolerated by the patient.

Marketing approval status

On 8th July 2020, it was announced that Biogen has submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for the approval of aducanumab. The completed submission followed ongoing collaboration with the FDA and includes clinical data from the Phase 3 EMERGE and ENGAGE studies, as well as the Phase 1b PRIME study. As part of the completed submission, Biogen has requested Priority Review.

This is the first jurisdiction to consider aducanumab.

https://investors.biogen.com/news-releases/news-release-details/biogen-completes-submission-biologics-license-application-fda

29. 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.

Aducanumab is currently an investigational product discovered by Neurimmune and licensed to Biogen, it does not currently have a trade name.

30. 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

31. 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 aducanumab on the PBS.

Changes in brain amyloid burden were exploratory endpoints in the aducanumab clinical trials.

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Patients who initially test negative may be tested again on follow up if no other underlying cause for their cognitive impairment can be ascertained.

Accessibility

There may be an accessibility issue for Aβ PET in some circumstances. If MSAC is willing to accept CSF AD biomarker assay as a secondary diagnostic for aducanumab eligibility, any access issue to Aβ PET is less significant as the lumbar puncture procedure can be performed to collect CSF specimens for *in vitro* testing.

32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Medical services that may be required concurrently with Aβ PET

- Administration of the amyloid radio tracer is assumed to be part of the Aβ PET service.
- If an Aβ PET was being performed on a CT/PET scanner, a concurrent CT scan would be required for attenuation purposes (It is suggested the MBS Item 61505 could be extended to include amyloid PET).

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).
- Under certain circumstances, imaging such as with an image intensifier or a CT scanner may be required to guide the lumbar puncture.

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

Aβ PET

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.

CSF AD biomarker testing

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.

Health professional who will order the tests

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.

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

Aβ PET

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.

CSF AD biomarker testing

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.

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

Health professional who will order the tests

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.

36. 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:

Aβ PET

With reference to the regulations on the MBS for delivering PET services for other diseases (i.e. "Note DIN Group I4 – Nuclear Medicine Imaging" for MBS Items 61523 to 61646), it is envisioned that 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.

^{18}F-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.

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

☒ Inpatient private hospital (admitted patient) - Aβ PET/LP specimen collection for CSF biomarker test
☒ Inpatient public hospital (admitted patient) - Aβ PET/LP specimen collection for CSF biomarker test
☒ Private outpatient clinic - Aβ PET/LP specimen collection for CSF biomarker test
☒ Public outpatient clinic – Aβ PET/LP specimen collection for CSF biomarker test
☐ Emergency Department
☐ Private consulting rooms - GP
☒ Private consulting rooms – specialist LP specimen collection for CSF biomarker test
☐ Private consulting rooms – other health practitioner (nurse or allied health)
☒ Private day surgery clinic (admitted patient) - Aβ PET/LP specimen collection for CSF biomarker test
☒ Private day surgery clinic (non-admitted patient) - Aβ PET/LP specimen collection for CSF biomarker test
☒ Public day surgery clinic (admitted patient) - Aβ PET/LP specimen collection for CSF biomarker
☒ Public day surgery clinic (non-admitted patient) - Aβ PET/LP specimen collection for CSF biomarker test
☐ Residential aged care facility
☐ Patient's home
☒ Laboratory – CSF biomarker test
☐ 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

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

☒ Yes
☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. 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 Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

The nominated comparator is "No testing for amyloid and therefore standard of care (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).

SoC for patients with a clinical diagnosis of mild AD would be treatment with acetylcholinesterase inhibitor (AChEI) therapy as first line AD medication and commercial nutritional supplements such as Souvenaid.

In the context of the co-dependency, the comparison is:

"Testing for amyloid and where the test is positive, use of aducanumab + SoC "

vs

"No testing for amyloid and therefore SoC".

Advice received from local clinicians indicated that patients already receiving symptomatic medication therapy who test positive for amyloid and go onto receive aducanumab would continue to also receive existing symptomatic medication. This is also consistent with the protocols for the pivotal clinical trials for aducanumab which permitted concomitant use of symptomatic therapies for AD.

40. 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

41. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

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 and commercial nutritional supplements such as Souvenaid.

A flow chart depicting the current clinical management pathway up to this point is provided in the Attachments REDACTED.

42. (a) Will the proposed medical service 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 instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

Current clinical management pathways
In current Australian practice, confirmatory biomarker testing is not required for patients with a clinical diagnosis of early stage AD.

Patients with a clinical diagnosis of MCI possibly due to AD are currently observed with instigation of brain health optimisation. This generally involves encouragement of physical activity and good nutrition, sometimes with the use of food supplements. *Note: medication therapy is not TGA indicated for patients with MCI.* Patients would be followed up over time (6-18 months [according to Laver 2016]). Those who subsequently progress to mild AD (i.e. have developed sufficient functional impairment to have dementia) may then be treated with AChEI therapy.

Patients with a clinical diagnosis of mild AD generally receive an AChEI therapy (e.g., donepezil) as a first line AD medication. AChEI therapy is PBS subsided for patients with mild to moderately severe AD.

Patients who subsequently progress to moderately severe AD may go on to receive a-methyl-D-aspartate receptor antagonist (NDMA RA) therapy, e.g. memantine either instead of or in addition to the AChEI, although only one of these therapies would be subsidised on the PBS.

Expected change as a consequence of introducing the proposed medical service
With the introduction of amyloid biomarker testing, patients newly clinically diagnosed as having early stage AD and also found to be positive for brain amyloid would be able to access aducanumab (provided all PBS eligibility criteria for the drug were met).
It is also proposed that patients previously diagnosed with mild AD and already receiving symptomatic treatment at the time of listing of aducanumab and found eligible for treatment with the new drug, including testing positive for the AD amyloid biomarker, would be permitted to continue to receive the existing SoC symptomatic therapy alongside aducanumab treatment.

Patients found to be brain amyloid negative would still be eligible to AChEI therapy, according to the PBS restriction. Alternatively, these patients could be investigated for other underlying causes of their cognitive impairment.

A flow chart showing current and proposed clinical management pathway is provided in Attachment 2

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. 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):

It is proposed that amyloid testing followed by aducanumab treatment is superior to no amyloid testing and current SoC for patients with early stage of 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 aducanumab 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).

45. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Health outcomes to be included in the evaluation of aducanumab for the treatment of patients with early stage AD are summarised below:

Safety Outcomes:

Co-dependent test safety

Aβ PET

Adverse events related to undergoing Aβ PET and exposure to Aβ PET ligands: the risk of adverse event is expected to be low

CSF AD biomarker testing

As an in vitro diagnostic test, there are no risks of adverse events related to CSF AD biomarker assay. However, there may be a small risk of adverse events related to the lumbar puncture procedure required to obtain the specimen for CSF biomarker testing.

Additionally, consideration of psychological harms from testing.

Co-dependent drug safety

Adverse events related to aducanumab and drug interactions will be detailed in the ADAR.

Clinical Effectiveness Outcomes:

Co-dependent test outcomes:

Aβ PET

- Test reliability/validity
- Test result concordance between different radiotracers for Aβ PET

Note: Aβ PET has previously been considered the gold standard test for antemortem detection of amyloid brain deposition and was employed in the pivotal trials for aducanumab. The test was used to provide confirmation of brain amyloid deposition to support the clinical diagnosis of AD. The intent of its use in clinical practice mirrors its use in the clinical trials from which the efficacy outcomes for aducanumab were observed, specifically in brain amyloid positive patients.

CSF AD biomarker testing

- Diagnostic accuracy (sensitivity/specificity/NPV/PPV) with Aβ PET as gold standard
- Test result concordance between commercially available CSF AD biomarker assays

Note: In the pivotal trials for aducanumab, a proportion of enrolled patients underwent both Aβ PET scanning and CSF AD biomarker testing in a sub-study.

Co-dependent drug efficacy outcomes:

As per the aducanumab clinical trials evidence:

Changes in: CDR-SB score (primary); MMSE; ADAS-Cog 13; ADCS-ADL-MCI (secondary)

Changes in AD biomarkers

Patient /caregiver reported outcomes Note these are key efficacy outcomes in the pivotal clinical trials evidence for aducanumab which will be presented in the ADAR.
Economic outcomes Change in patient management due to amyloid testing Quality of life and QALYs of patients and carers Lost productivity of patients and carers Impact on entry to community care and nursing home facilities Incremental cost per QALY gained ratios (with and without indirect/productivity/carer costs)

Aβ, beta-amyloid; AD, Alzheimer disease; ADAR, Applicant Developed Assessment Report; ADAS-Cog-13, Alzheimer Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR-SB, Clinical Dementia Rating sum of boxes; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; QALY, quality-adjusted life-year.

The key health outcomes to be presented in the ADAR will be provided by three clinical trials of the co-dependent drug intervention, aducanumab, a phase 1 study (PRIME) and two phase 3 studies (EMERGE and ENGAGE). The EMERGE and ENGAGE trials will be considered the pivotal evidence.

A full account of the EMERGE and ENGAGE studies is yet to be finalised and published formally. However results have been made available in the public domain (https://www.veracast.com/webcasts/clients/webcasts/v/0C1CC820A65F.cfm#/player/html5/speed/v150; https://investors.biogen.com/news-releases/news-release-details/biogen-completes-submission-biologics-license-application-fda).

The following provides a brief summary of the design of the trial which may assist in the development of the PICO protocol for the assessment.

EMERGE and ENGAGE study design

The EMERGE and ENGAGE studies were identical multicentre, double-blind, placebo-controlled parallel group Phase 3 studies (Table 4). For inclusion into the trials, subjects had to be aged 50-85 years, meet the NIA-AA clinical diagnostic criteria for MCI due to AD/prodromal AD or mild AD (Albert 2011; McKhann 2011), have a MMSE score of 24-30, CDR-GS of 0.5, RBANS score ≤ 85 and a positive Aβ PET scan. Subjects were randomised to receive either a low or high dose of aducanumab or placebo. Treatment was administered by intravenous infusion on a monthly basis for 78 weeks. The primary outcome measure was the change from baseline in Clinical Dementia Rating sum of boxes (CDR-SB) at week 78. Additional outcome measures included other clinical measures of cognitive and functional impairment, patient/caregiver reported outcomes, changes in AD biomarkers (as determined by Aβ PET and/or CSF AD biomarker testing) and safety outcomes, including amyloid-related imaging abnormalities (ARIA).

Table 4 Key design characteristics of the EMERGE and ENGAGE trials

Trial ID	Trial design	Population – key inclusion criteria	Intervention and comparator	Key outcome measures
EMERGE (N=1638) ENGAGE (N=1647)	Both trials were: Phase 3, MC, R (1:1:1), DB, PC PG	• MCI due to AD OR mild AD dementia, based on clinical criteria • Age 50 -85 years • MMSE 24-30 • CDR GS = 0.5 • RBANS ≤ 85 • Confirmed amyloid pathology (**as**	• Aducanumab low dose (titrated to 3 or 6 mg/kg*) • Aducanumab high dose (titrated to 6 or 10 mg/kg*,**) • Placebo Treatments were administered monthly	**Primary outcome** Change from baseline in CDR-SB (primary endpoint at 78 weeks) **Secondary outcomes** Change from baseline in: • MMSE • ADAS-Cog-13

Trial ID	Trial design	Population – key inclusion criteria	Intervention and comparator	Key outcome measures
		determined by positive Aβ PET scan)	by intravenous infusion Treatment duration was up to 78 weeks	• ADCS-ADL-MCI **Biomarkers (exploratory):** • Aβ (as determined by Aβ PET) • CSF biomarker proteins **Safety including**: • Incidence of all AEs and SAEs • Brain MRI findings (including incidence of ARIA-E and ARIA-H)

Aβ, beta-amyloid ; AD, Alzheimer disease; ADAS-Cog-13, Alzheimer Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version); ARIA-E, amyloid-related imaging abnormality-oedema; ARIA-H, amyloid-related imaging abnormality- haemosiderin; CDR-GS, Clinical Dementia Rating Global Scale; CDR-SB, Clinical Dementia Rating sum of boxes; CSF, cerebrospinal fluid; DB, double-blind; MC, multicentre; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; PG, parallel group; PC, placebo -controlled; R, randomised; RBANS, Repeatable Battery for Assessment of Neuropsychological Status

*Dependent on Apolipoprotein E (ApOE ε4) carrier status;
**Dependent on protocol version; all subjects randomised to high dose after protocol version 4 received 10 mg/kg

Sources:
https://investors.biogen.com/static-files/ddd45672-9c7e-4c99-8a06-3b557697c06f;
https://clinicaltrials.gov/ct2/show/NCT02484547?term=aducanumab&draw=2&rank=6
https://clinicaltrials.gov/ct2/show/NCT02477800?term=aducanumab&draw=2&rank=7

In summary, aducanumab has shown to slow AD disease progression and reduce Aβ plaque burden in patients clinically diagnosed as having MCI due to AD/prodromal AD or mild AD, which was confirmed by testing positive for amyloid brain pathology. Aducanumab has also been shown to be well tolerated in this patient population.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

47. Estimate the prevalence and/or incidence of the proposed population:

The condition targeted in this application is early stage AD, which includes patients with MCI or mild AD.

AD biomarker testing will be utilised in patients clinically diagnosed with early stage AD and aducanumab used subsequently in eligible patients. These two populations 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 dementia from MCI being the significant interference in the ability to function at work or in usual daily activities (that is dementia). 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 populations 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 an ADAR.

The application presents a top down approach for estimating the prevalence of mild AD and MCI patients in Australia (see Table 5). Prevalence of mild AD is informed by the National Centre for Social and Economic Modelling (NATSEM) 2017 report (Brown 2017) which utilised a standard demographic modelling approach in which age-sex dementia prevalence rates are applied to age-sex population projection estimates. The prevalence rates for older cases (i.e. those aged 65+ years) were derived from the pooled, harmonised, dataset from DYNOPTA reported by Anstey and colleagues (2010). The prevalence rates for the younger onset dementia age group were those used by Australian Institute of Health and Welfare (AIHW) in their 2012 report. 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). The prevalence of MCI patients was based on the prevalence of amnesic MCI patients reported in Sachdev (2014) 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. Finally, the proportion of mild dementia and MCI patients with AD dementia sub-type was assumed to be 76% and 75% respectively, based on Knopman (2016), although it should be noted that this estimate is not widely reported in the literature and will be clarified in the ADAR.

When a clinical diagnosis of either 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.**

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Table 5 Epidemiological inputs for determining proportion of mild AD and MCI eligible for aducanumab

Parameter	Value	Source
Mild AD population		
Prevalent dementia patient population in Australia	Approximately 500,000	NATSEM dementia Australia report (Brown 2017), Appendix 1, pg.54
Proportion of patients 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
REDACTED	**REDACTED**	**REDACTED**

Parameter	Value	Source
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
MCI population		
Australian population 50+ without dementia	Approximately 8,000,000	ABS data and dementia prevalence estimates reported in the NATSEM dementia Australia report (Brown 2017), Append 1 pg.54
Proportion of 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
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**
REDCATED	**REDACTED**	**REDACTED**
REDACTED	**REDACTED**	**REDACTED**

48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

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

REDACTED

Administration of aducanumab via intravenous infusion is according to a dosing regimen of once per month.

See also, answer to Q31.

49. How many years would the proposed medical service(s) be required for the patient?

See also answer to Q48.

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

Table 6 presents estimates for the first full year of listing, 2021. Uptake of aducanumab has not been estimated for the application but will be presented in the co-dependent ADAR.

51. Estimate the anticipated uptake of the proposed medical service 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 6 presents estimates for the first three years of listing, namely 2021 to 2023. Uptake of aducanumab has not been estimated for the application but will be presented in the ADAR. 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. **REDACTED** 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 aducanumab 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 6 Estimated number of mild AD and MCI eligible for aducanumab patients in the first years of listing

Row	Parameter	2021	2022	2023	Calculation/Source
		(1ST year)	(2nd year)	(3rd year)	
	Mild AD population				
A	Prevalent dementia patient population in Australia	467,401	484,408	501,015	NATSEM 2017
B	Number of patients with mild dementia	257,071	266,424	275,558	A x 55%, AIHW 2012
C	Number of mild dementia patients with suspected AD	195,374	202,483	209,424	B x 76%, Knopman 2016
D	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
E	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
F	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
G	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
H	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
	MCI population				
I	Australian population 50+	8,865,837	9,052,316	9,224,990	ABS data

J	Prevalent dementia population	467,401	484,408	501,015	NATSEM report
K	Australian population 50+ without dementia	8,398,436	8,567,908	8,723,975	I – J
L	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
M	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
N	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
O	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
P	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
Q	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**
R	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**	**REDACTED**

PART 8 – COST INFORMATION

52. 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 (R)). This was MBS fee 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 Sponsor is currently seeking advice from producers of radiotracers in Australia regarding the cost of producing the FDG and Aβ PET ligands. This is intended to cover the majority of costs associated with the AD biomarker test including the Aβ PET ligand, PET scan and Aβ PET interpretation. In addition, a concurrent CT scan would be required for attenuation purposes (it is suggested the MBS Item 61505 could be extended to include amyloid PET. 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. Costs associated with biomarker testing and administration of aducanumab are summarised in Table 7.p

Table 7 Costs associated with biomarker testing and administration of aducanumab

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.
Use of PET/CT scanner for Aβ PET	TBD	$100.00	MBS item 61505
CSF biomarker test			
Lumbar puncture	1	$197.10	MBS items 21945, 39000, 23010
Day Private Hospital Charge	1	$550.00	Assumption based on cost of Minor Medical Procedures ($720; Tier 2; 1013) excluding the pathology cost ($168)
CSF Test Assay	1	$250.00	Price of test assay for AD screen of three proteins by the National Dementia Diagnostics Laboratory
Aducanumab			
Intravenous infusion of immunomodulating agent	1	$99.50	MBS item 14245

53. Specify how long the proposed medical service 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.

Aducanumab is administered to patients by intravenous infusion on a monthly basis. The expected infusion time is approximately 1 hour.

54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Proposed wording for the proposed MBS item descriptors for Aβ PET and CSF biomarker testing is provided below:

Category 5 – DIAGNOSTIC IMAGING SERVICES
Beta-amyloid positron emission tomography (PET) study of the brain, performed for the evaluation of a patient with a clinical diagnosis of early stage Alzheimer disease, requested by the specialist or consultant physician who manages the treatment of the patient, to determine if the requirements relating to the amyloid status for access to aducanumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. The patient considered for this service must also meet specific PBS eligibility criteria for treatment with aducanumab other than the criterion relating to amyloid status. MBS Fee: $### Benefit: 75% = $#### 85% = $###
Category 6 - PATHOLOGY SERVICES
Quantitation, by immunoassay methodology, of amyloid and tau proteins in cerebrospinal fluid from a patient with a clinical diagnosis of early stage Alzheimer disease, requested by the specialist or consultant physician who manages the treatment of the patient, to determine if the requirements relating to the amyloid status for access to aducanumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. The patient considered for this service must also meet specific PBS eligibility criteria for treatment with aducanumab other than the criterion relating to amyloid status. MBS Fee: $### Benefit: 75% = $#### 85% = $###

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Attachments

REDACTED