Australian Government

Department of Health

Second PASC consideration- Ratified PICO Confirmation

Application 1643:

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

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	**Test 1 and 2**: Patients with a diagnosis of "early stage" Alzheimer's disease (AD), comprising mild cognitive impairment (MCI) due to AD/prodromal AD *OR* mild AD dementia, based on core criteria for AD, clinical assessment, and structural imaging. **Treatment:** Patients with early stage AD (as defined above) and evidence of beta-amyloid (Aβ) deposition in the brain confirmed either by Aβ positron emission tomography (PET) scanning or cerebrospinal fluid (CSF) AD biomarker testing.
Prior tests (for investigative medical services only)	Cognitive and functional tests; blood tests; structural imaging using computerised tomography (CT) or magnetic resonance imaging (MRI); possible further neuropsychological assessment with validated instruments. Functional imaging using single proton emission computerised tomography (SPECT) or fluorodeoxyglucose (FDG) PET where AD diagnosis is uncertain/atypical after above assessments.
Intervention	**Test 1:** Brain Aβ PET scan OR **Test 2:** CSF AD biomarker testing **Treatment:** Aducanumab + Standard of care (SoC) defined as non-pharmacological interventions to optimise brain health (e.g. activity, cognitive training, and diet) and/or, for patients with mild AD, acetylcholine esterase inhibitor (AChEI) therapy **Codependence:** Access to aducanumab for patients who meet the PBS requirements for early stage AD with confirmed brain Aβ deposition by either Aβ PET scanning or CSF AD biomarker testing.
Comparator	**Test 1:** • No testing for Aβ deposition (current practice) • FDG PET **Test 2:** • No testing for Aβ deposition (current practice) • Aβ PET scanning

Component	Description
	Treatment: SoC (AChEI therapy and/or non-pharmacological interventions to optimise brain health)
Evidentiary standard	Aβ PET scanning to confirm Aβ pathology conducted as per screening for inclusion in the aducanumab Phase III studies EMERGE/ENGAGE. The evidentiary standard includes the circumstances of testing including centralised visual read, the particular radiopharmaceuticals used, and the scan criteria for eligibility of participants as applied in the Phase III trials.
Outcomes	**Test 1 and Test 2** (see Outcomes section for details) • Safety (adverse events from testing procedures including radiation dosimetry and lumbar puncture for Aβ PET and CSF AD biomarker testing, respectively) • Extent of positive and negative discordance between Aβ PET scanning as conducted in Australia and the evidentiary standard • Extent of positive and negative discordance between CSF AD biomarker testing as conducted in Australia and the evidentiary standard • Yield of testing (proportion of patients identified as having brain Aβ deposition) • Change in management **Treatment** (see Outcomes section for details) Safety and tolerability • Treatment-related amyloid-related imaging abnormality-(o)edema (ARIA-E) and amyloid-related imaging abnormality-haemorrhage (ARIA-H) events Clinical effectiveness • Cognitive, behavioural, and functional impairment (both as an absolute measure and as the rate of decline over time) • Ability to perform tasks for daily living • Treatment response rate (proportion of patients with significant change in cognitive and functional impairment, both as an absolute measure and as the rate of decline over time) • Duration of treatment response • Rates of hospitalisation • Mortality • Quality of life • Patient/carer reported outcomes • Time to admission to full-time care

Component	Description
	Healthcare system • Utilisation • Healthcare costs • Cost-effectiveness/cost-utility including a comparison of the two testing methods Aβ PET and CSF AD biomarker testing • Total cost to MBS and PBS

MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme

PICO or PPICO rationale for therapeutic and investigative medical services only[1]

Background

This PICO was initially considered by the PICO Advisory Subcommittee (PASC) in December 2020. Following its first consideration, two outstanding issues were identified as requiring resolution before a ratified PICO could be endorsed by the Committee. These were:

- *what threshold standardised uptake value ratio (SUVR) or Centiloid value would be proposed to match the improved inter-rater reliability achieved by the centralised visual reads of the Aβ PET scans used to confirm eligibility of participants into the EMERGE/ENGAGE studies; and*
- *MSAC's advice regarding MBS funding of FDG PET for AD.*

PASC considered these issues could be addressed at the subsequent April 2021 PASC meeting.

Population

The population of relevance to the PICO are patients with a diagnosis of early stage AD based on core criteria for AD, clinical assessment, and structural imaging. Patients in this population would be eligible for access to PBS subsidised aducanumab treatment if they have Aβ deposition in the brain confirmed by one of the two proposed test options, Aβ PET scanning or CSF AD biomarker testing. Deposition of Aβ in the brain provides supportive evidence of an AD diagnosis and is the target of the codependent drug, aducanumab.

Patients eligible for either of the two tests should have a diagnosis of early stage AD (defined as "mild cognitive impairment (MCI) due to AD/prodromal AD *OR* mild AD dementia" according to the National Institute on Aging and Alzheimer's Association (NIA-AA) and International Working Group (IWG) guidelines), based on the core criteria for AD, clinical assessments and structural imaging of the brain (Albert et al. 2011; Dubois et al. 2010; Dubois et al. 2007; McKhann et al. 2011).

[1] Common abbreviations used in this document: MSAC – Medical Services Advisory Committee; PBAC – Pharmaceutical Benefits Advisory Committee; MBS – Medicare Benefits Schedule; PBS – Pharmaceutical Benefits Scheme; PASC – PICO Advisory Subcommittee; PICO – Population, Intervention, Comparator, Outcome.

At its December 2021 meeting, PASC noted that the population is patients with early stage AD, which includes patients with:

- *MCI due to AD*
- *prodromal AD*
- *mild AD dementia.*

PASC noted that a positive CSF biomarker test was not an inclusion criterion for the ENGAGE/EMERGE trials.

The applicant noted that the terms 'MCI due to AD' and 'prodromal AD' refer to the same subgroup of early-stage AD patients and that these terms are used interchangeably in the literature.

PASC noted the applicant's April 2021 pre-PASC response, which stated that there is an intended difference in the patient population to be tested and the patient population that is to receive treatment with aducanumab. At the April 2021 PASC meeting, the applicant clarified that it intended the eligible population for biomarker confirmation would be:

- *mild cognitive impairment (MCI) suspected due to AD; or*
- *mild dementia.*

This differs from the applicant's proposed population for eligibility to aducanumab:

- *MCI due to AD; or*
- *mild AD dementia.*

PASC noted the patient population identified for biomarker testing differs from that agreed to at the December 2020 PASC meeting. Specifically, the population now nominated by the applicant includes patients with MCI suspected to be due to AD, whereas the initial population considered eligible for testing included "Patients with a diagnosis of "early stage" Alzheimer's disease (AD), comprising mild cognitive impairment (MCI) due to AD/prodromal AD OR mild AD dementia, based on core criteria for AD, clinical assessment, and structural imaging." PASC did not support this change to the population for testing, given it greatly expands the eligible population and would allow for Aβ PET scanning and CSF AD biomarker testing to be utilised for diagnosing AD as opposed to being a test used to establish eligibility for access to aducanumab on the PBS.

PASC considered the possibility of requiring diagnosis of AD via FDG-PET as a prerequisite to Aβ PET scanning and CSF AD biomarker testing. The applicant's clinical expert advised that with a specificity of 70% against Aβ PET (which reduces with increasing age), this prior use of FDG-PET would be expected to exclude many patients who would be truly eligible for aducanumab according to the Aβ PET result. In addition, for many patients, the cost and time of FDG-PET scanning would simply be added to the cost and time of the confirmatory Aβ PET or CSF AD biomarker. On balance, PASC advised that FDG-PET should remain an option for diagnosing AD, but it should not be a prerequisite to the proposed testing.

In addition, patient eligibility for testing would also be conditional on meeting any additional PBS-specific eligibility criteria for treatment with the codependent drug, aducanumab, other than verification of Aβ deposition in the brain. Patients diagnosed with moderate or severe AD would not be eligible for the proposed tests because they would not meet the anticipated eligibility criteria for

treatment with aducanumab on the PBS. No other patient populations would be eligible for the proposed tests.

Alzheimer's disease is an incurable progressive neurodegenerative disorder characterised by gradual and unrelenting decline in cognition and increased behavioural disturbances. Patients with AD become increasingly reliant on caregivers as the disease progresses, with full-time care required as the patient transitions to the severe stage of the disease.

Pathologically, AD is defined by the presence of extracellular neuritic plaques in the brain containing Aβ peptide and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau proteins. Evidence suggests the pathophysiological changes begin up to 20 years before clinical onset of AD. Development of Aβ plaques and neurofibrillary tangles occurs in a preclinical phase of AD. Their accumulation over time leads to synapse dysfunction and loss of neurons, at which point early signs of cognitive impairment become apparent. As AD progresses, gross atrophy occurs in specific regions of the brain, leading to progressive cognitive decline (Hardy & Selkoe 2002; Jack et al. 2013).

The stages of AD as defined by the NIA-AA and IWG guidelines are:

- Preclinical AD
- MCI due to AD/prodromal AD
- Mild AD dementia
- Moderate AD dementia
- Severe AD dementia

MCI due to AD/prodromal AD is the earliest symptomatic phase prior to the onset of dementia. There are no clear boundaries between the different stages of AD as the disease progresses on a continuum. The severity of cognitive impairment or dementia can be staged using widely accepted clinical cognitive or neuropsychological assessments, such as the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) (Folstein, Folstein & McHugh 1975; Morris 1993). However, differentiation of MCI from mild dementia is often based on clinical judgment of a dementia specialist through assessment of the individual and reports of carers/family members. The applicant indicated that the extent of overlap between the MCI and mild AD dementia patient populations will be discussed in the Applicant Developed Assessment Report (ADAR).

Alzheimer's disease accounts for 50–70% of all cases of dementia (Rizzuto et al. 2012; Winblad et al. 2016). The prevalence of AD and other forms of dementia increase 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 (Australian Institute of Health and Welfare 2012). In 2020, there were 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. Based on the above figures for 2020, it can be estimated that approximately 230,000–321,000 individuals have AD dementia in Australia.

Using data from the National Centre For Social And Economic Modelling and the AIHW, the applicant estimated that 125,000 individuals would have MCI due to AD/prodromal AD and 195,000

individuals would have mild AD dementia in Australia in 2021 (see Table 6; page 13 of the Application form).

Rationale

The population of interest is the same patient population included in the aducanumab Phase III studies, EMERGE and ENGAGE. In these studies, the efficacy of aducanumab was demonstrated in patients with MCI due to AD/prodromal AD or mild AD dementia, and with Aβ deposition in the brain confirmed by Aβ PET. Aβ deposition in the brain confirmed by Aβ PET scanning was required for study eligibility. Assessment of CSF AD biomarkers as a proxy for Aβ deposition in the brain was not used to determine eligibility for EMERGE/ENGAGE.

A regulatory submission seeking TGA approval and listing on the ARTG for aducanumab is planned in early 2021. Additionally, the applicant has submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for the approval of aducanumab under Priority Review. The FDA submission includes clinical data from the Phase III EMERGE (NCT02484547) and ENGAGE (NCT02477800) studies, as well as the Phase Ib PRIME (NCT01677572) study (Sevigny et al. 2016, 2017). The TGA submission (and applications to MSAC/ Pharmaceutical Benefits Advisory Committee (PBAC)) will be based on evidence from the Phase III studies EMERGE and ENGAGE.

In Australia, confirmation of suspected dementia (including AD) would initially involve consultation with a general practitioner (GP). A patient history would be taken, along with a comprehensive physical examination and basic cognitive assessments (RACGP, 2012). Patients with suspected AD are then referred to a memory clinic, gerontologist, or specialist in dementia. Diagnosis of AD is predominantly based on clinical findings, cognitive/neuropsychological assessments, and structural imaging of the brain by computerised tomography (CT) or magnetic resonance imaging (MRI). Evidence suggests this approach is around 70% accurate in mild AD dementia and 50-60% accurate for individuals with MCI due to AD/prodromal AD (Beach et al. 2012; Knopman et al. 2001). Confirmation of Aβ deposition in the brain and/or changes in CSF levels of AD biomarkers may provide supportive evidence for an AD diagnosis, as recognised in the IWG and NIA-AA guidelines (Albert et al. 2011; Dubois et al. 2010; McKhann et al. 2011).

Neuropsychological tests outcomes used to define the early stage AD population for inclusion in the Phase III EMERGE/ENGAGE studies were:

- Clinical Dementia Rating Global score (CDR-G) of 0.5
- Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score ≤ 85 indicative of objective cognitive impairment (based upon the Delayed Memory Index score)
- MMSE score 24–30 (inclusive).

In these studies, ~80% patients had MCI due to AD/prodromal AD and 20% had mild AD dementia; all patients had brain Aβ deposition confirmed by Aβ PET scanning. Further information is required about the baseline characteristics of patients in the Phase III study EMERGE that responded to aducanumab treatment and whether their baseline characteristics are representative of the study ITT population. Treatment efficacy was only confirmed by one Phase III study, EMERGE.

In the Phase Ib study (PRIME), criteria for prodromal AD were: MMSE score 24–30, a spontaneous memory complaint, objective memory loss defined as a free recall score of ≤27 on the Free and Cued Selective Reminding Test, CDR-G score of 0.5, absence of significant levels of impairment in other cognitive domains and essentially preserved activities of daily living, and an absence of dementia. The criteria for mild AD dementia were: MMSE score 20–26, CDR-G score of 0.5 or 1.0, and meeting the NIA-AA core clinical criteria for probable AD.

Prior tests

Over several consultations, a GP will have obtained a complete medical history and performed a comprehensive physical examination. A number of screening instruments are used to assess cognitive and functional status, but consideration of the full clinical presentation is important.

Cognitive and functional assessment instruments used in Australia are:

- MMSE
- General Practitioner Assessment of Cognition
- Clock drawing test
- Rowland Universal Dementia Assessment Scale
- The Instrumental Activities of Daily Living.

After GP assessment, patients with suspected AD would be referred to a specialist for further assessment to confirm the diagnosis. Patients eligible for either Aβ PET scanning or CSF AD biomarker testing would already have undergone clinical assessment by a specialist to establish a diagnosis of early stage AD. Further investigative tests carried out by the specialist could include:

- blood tests (full blood count; urea and other electrolytes, liver function tests, calcium, thyroid function tests, serum vitamin B12 and folate)
- structural brain imaging (e.g. CT or MRI)
- further cognitive/neuropsychological testing for impairment
- possible functional imaging with cerebral perfusion SPECT or FDG PET when the diagnosis of AD is uncertain/atypical.

Interventions

The Application proposes two testing options, Aβ PET and CSF AD biomarker testing, either of which could be used to determine whether a patient with a clinical diagnosis of early stage AD would be eligible for the codependent drug, aducanumab, on the PBS. *PASC noted that this Application is an integrated codependent submission between MSAC and the PBAC for treatment with aducanumab after a positive Aβ PET scan or CSF biomarker test result for AD.*

The tests are proposed to confirm the presence of Aβ deposition in the brain and hence AD pathology as the underlying cause of the condition. The two proposed tests are presented as alternative options to determine eligibility for aducanumab treatment and are intended to be mutually exclusive. Only one test option per patient would be reimbursed to determine aducanumab treatment eligibility and testing frequency is once per lifetime. The applicant is not proposing either of these tests as diagnostic services*. PASC noted that a cerebral perfusion SPECT*

scan (MBS item 61402) is the only test currently reimbursed on the MBS which can be used for the diagnosis of AD.

The extent of positive and negative discordance of each of these testing options available in Australia will need to be assessed against the evidentiary standard involving Aβ PET in order to confirm their clinical utility.

Aβ PET

PET is a minimally invasive diagnostic imaging technique and the only ante-mortem technique that can directly confirm the presence of Aβ pathology in the brain. Aβ PET imaging employs an intravenously administered radioisotope labelled tracer that travels to the brain and selectively binds Aβ plaques. The relative differences in the rate of the tracer decay within the different anatomical regions of the brain provides information about the density and location of the Aβ plaques within the brain. Images are considered as either "amyloid-positive" or "amyloid-negative" based on visual scan assessment of tracer uptake in the grey matter. The specific criteria for Aβ PET image interpretation differs among available radiopharmaceuticals (Landau et al. 2014). It is therefore important that scan images are visually interpreted only by expert readers who have successfully completed the appropriate training provided by the manufacturer of the radiopharmaceutical being used.

There are currently 85 Medicare eligible PET scanning facilities in Australia. Aβ PET scanning is not currently funded on the MBS. Aβ PET scans may be acquired using PET, PET/CT, or PET/ MR systems from various manufacturers. Use of a PET/CT scanner permits CT based attenuation correction for quantitative PET imaging. Alternatively, attenuation correction using an attenuation source or calculated attenuation correction is required.

PASC noted that Aβ PET scanning is always performed with a CT (PET/CT) or MRI (PET/MRI), both for accurate anatomic localisation and for attenuation correction. PASC noted there is an existing MBS item available for concurrent PET/CT (MBS item 61505), however there is no MBS item available for concurrent PET/MRI.

Currently, no radiopharmaceutical for Aβ PET has been approved by the TGA. Three ^{18}F-labelled tracers for Aβ PET (^{18}F-florbetapir; ^{18}F-florbetaben; and ^{18}F-flutemetamol) are commercially available and have regulatory approval in jurisdictions outside of Australia (e.g., US and Europe). In Australia, Cyclotek has validated the manufacture of the three Aβ radiopharmaceuticals, ^{18}F-florbetaben (Neuraceq®), ^{18}F-florbetapir (Amyvid®) and ^{18}F-flutemetamol (Vizamyl®) for use in clinical trials in Australia and New Zealand and available through the Special Access Scheme. Other producers of Aβ PET radiopharmaceuticals in Australia include hospital nuclear medicine departments with onsite cyclotrons. Manufacturing standards across local producers of Aβ PET tracers can vary as local hospitals do not require a Good Manufacturing Practice license, which is mandatory for commercial companies. Another radiopharmaceutical, ^{18}F-flutafuranol or NAV4694, 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. It is used for research and currently has limited clinical use although it is under development for wider commercial use.

PASC noted that the following Aβ radiopharmaceuticals are used in Australia: ^{11}C-PiB (Pittsburgh compound B), ^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben and ^{18}F-flutafuranol, but none is TGA-approved. PASC noted that ^{18}F-flutafuranol is not FDA-approved and was not available for use as an inclusion criterion in the aducanumab trials.

PASC noted that, although not in scope for the Application, tau radiopharmaceuticals are also available, and that ^{18}F-flortaucipir is FDA approved and has been used in Australia.

PASC noted that ^{11}C-PiB was the prototype and is associated with less non-specific white matter labelling than the "first generation" ^{18}F-labelled agents (florbetabir, flutemetamol and florbetaben), but that the short half-life of C-11 (20 min) rendered this agent unsuitable for widespread use; ^{18}F-flutafuranol – a "second-generation" agent – more closely mimics the distribution of ^{11}C-PiB. However, PASC was advised that, for visual assessment, all the radiopharmaceuticals proposed could be considered interchangeable, with the expectation that the evidence supporting this interim conclusion will be provided in the integrated codependent submission for MSAC consideration.

As per the protocols of the aducanumab studies (EMERGE/ENGAGE), subjects must have a positive amyloid PET scan read centrally (as defined by the visual reading process established by the selected amyloid tracer's methodology) at study screening to be eligible for the trial. The central amyloid PET eligibility review in each of the Phase 3 studies used a pool of three central neuroradiologists trained in the visual read assessment of the three amyloid tracers (18F-florbetapir, 18F-flutemetamol, 18F-florbetaben) as established by the respective tracer manufacturer and described in the product package insert (where approved). Each screening amyloid PET scan was assigned and visually read by a single neuroradiologist from the pool of three readers to obtain a binary visual assessment (positive or negative) of the amyloid status of each subject.

The Application suggested that the proposed Aβ PET scan service should include Aβ quantification as measured using a standardised uptake value ratio (SUVR) and preferably using the Centiloid scale. In Aβ PET, causes of variability in quantitatively expressed outcome data include the particular β radiopharmaceutical used, acquisition time duration, method of analysis, target and reference regions employed, and the PET scanner (e.g., scanner model, reconstruction algorithm and method of attenuation correction) (Klunk et al. 2015). Quantification using SUVR units is impacted by these causes of variability. In Aβ PET scanning, the SUVR unit is an estimate of brain Aβ burden and is the ratio of radiopharmaceutical uptake in brain regions of interest (typically in regions with Aβ pathology) to radiopharmaceutical uptake in a reference region (typically in brain regions with no or minimal Aβ pathology). The Centiloid scale was developed for use in clinical studies where imaging is carried out using different radiopharmaceuticals across multiple study sites. However, the Centiloid scale still cannot adjust for variability associated with different PET scanners (Klunk et al. 2015). Quantitative Aβ imaging measures are standardised by transformation of SUVR values into Centiloid values using equations specific to each PET radiopharmaceutical. The Centiloid scale is a linear scale where zero represents "high certainty" Aβ-negative subjects and 100 is consistent with mild to moderate AD dementia. Studies have proposed Centiloid threshold values for Aβ pathology associated with Aβ burden at different stages of AD. For example, Amadoru et al (2020) proposed that 26 Centiloids correlated with the positive or negative threshold of an Aβ PET scan visually assessed by an expert reader. A threshold of 20 Centiloids or lower reflected the absence of moderate or frequent plaques by neuropathologic evaluation of the brain at post-mortem (Amadoru

et al, 2020). Imaging experts confirmed that a Centiloid threshold of >50 would be consistent with an AD diagnosis, which is in line with the findings of Amadoru et al (2020). Any threshold of SUVR or Centiloid value proposed for confirming positive Aβ pathology and eligibility for aducanumab treatment in Australia should have an evidentiary basis demonstrating that the intended improvement in inter-rater reliability of visual reads across Australia would accurately match the centralised visual reads used to confirm eligibility of participants into the EMERGE/ENGAGE studies.

For amyloid pathology confirmation at screening (one of the study inclusion criteria), the Phase III studies EMERGE/ENGAGE permitted use of three different Aβ PET radiopharmaceuticals, Amyvid™ (^{18}F-florbetapir), Vizamyl™ (^{18}F-flutemetamol), or Neuraceq™ (^{18}F-florbetaben). In the EMERGE/ENGAGE Aβ PET sub-studies, the applicant confirmed that Aβ PET was carried out with ^{18}F-florbetapir in the EMERGE/ENGAGE studies except for a small number of patients in Japan where ^{18}F-flutemetamol was used. Aβ PET scan data obtained during EMERGE/ENGAGE Aβ PET sub-studies, was standardised used SUVR. The applicant indicated that only study data from Japan in EMERGE/ENGAGE was converted from SUVR to Centiloid values due to the use of two radiopharmaceuticals, ^{18}F-florbetapir and ^{18}F-flutemetamol, across study sites. The Application did not include information regarding the specific cut-off values/thresholds used to differentiate between positive and negative Aβ pathology in the brain using Aβ PET and there was no information in the study protocol for EMERGE or ENGAGE. Visual assessment of Aβ PET scans by expert readers was used to determine Aβ pathology in the brain as positive or negative. The applicant indicated that further information about the assessment process will be provided in the ADAR.

For visual assessment, PASC advised that Aβ PET has improved inter-rater concordance against visual reads when interpreted using semiquantitative measures of uptake such as the standardised uptake value ratio (SUVR) or the Centiloid scale. PASC also noted that, while such quantification can improve inter-rater concordance for positive and negative scan results, "intermediate" results can also occur, where the diagnosis of AD dementia remains uncertain. PASC noted that there was no mention as to how such results would be handled. The applicant noted its clinical expert's opinion that it is relatively rare for an "intermediate" result to occur, but confirmed that this could be further investigated in the assessment report.

Following PASC's initial consideration in December 2020, the applicant proposed in its April 2021 pre-PASC comments, that while semiquantitative methods could be used to interpret the Aβ PET scan results, it did not intend to mandate their use in the proposed MBS item descriptor or assessment report. Instead, the applicant proposed the MBS item descriptor could include the following method agnostic wording in relation to semiquantitative assessment, "with or without quantitative assessment". PASC questioned whether this inclusion would add further meaning to the intended users of the item descriptor.

The applicant acknowledged that, as a semiquantitative approach would not be mandated, the integrated codependent submission would address the issue of reduced confidence in the comparative accuracy of Australian non-centralised visual reads compared with the evidentiary standard of centralised visual reads due to expected reduced inter-rater reliability. If one or other identified semiquantitative approach is subsequently proposed, the proposed threshold(s) for positivity for eligibility to aducanumab would also need to be defined for inclusion in the proposed PBS restriction as advised by PASC in its initial consideration.

PASC noted that one suggestion made to minimise the extent of inter-rater variability would be to require that the Aβ PET scans are only read by those who have successfully completed appropriate training by the manufacturer of the radiopharmaceutical used or by another appropriate body. PASC considered it remained unclear how such a training program would be implemented given none of the four radiopharmaceuticals used is TGA approved or manufactured on a commercial scale. Therefore, issues would arise from this suggestion regarding who would be responsible for implementing, accrediting and managing this type of training program, and ensuring that it can be linked as a prerequisite to the practitioner's ability to bill the MBS for the service.

The applicant's clinical expert noted that training modules are available and must be completed prior to ordering the Aβ PET radiopharmaceuticals from overseas, and clarified that Australian nuclear medicine physicians can access these training modules. The clinical expert also noted there is currently no training module available for one of the radiopharmaceuticals produced in Australia, 18F-flutafuranol or NAV4694, however development of training modules for this is in progress. Following the development of these training modules, the clinical expert explained the intention would then be for those who have undertaken the training in the next few months to be provided with Aβ PET scans from the EMERGE/ENGAGE trial and the outcomes of their reads to be compared to the outcomes of the centralised reads performed in the trial. The applicant confirmed that they would explore data access and whether these comparative data could then be made available to MSAC in the assessment report.

<u>CSF AD biomarker testing</u>

CSF AD biomarker testing is performed using *in vitro* immunoassays. The CSF sample is obtained by lumbar puncture using a standardised collection procedure. Levels of specific biomarkers (Aβ 1-42 peptides, total tau, and phosphorylated tau) in the sample are then quantified using the *in vitro* immunoassay, and positivity or negativity for Aβ deposition in the brain can be determined using cut-offs/thresholds validated using Aβ PET.

PASC noted the proposed NIA-AA "AT(N)" classification of CSF biomarkers in AD (Jack et al. 2018):

> *A: Aggregated Aβ or associated pathogenic state (CSF $Aβ_{1-42}$, or $Aβ_{1-42}$/ $Aβ_{1-40}$ ratio);*
>
> *T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau [p-Tau] or p-Tau/$Aβ_{1-42}$ ratio); and*
>
> *(N): Neurodegeneration or neuronal injury (CSF total tau [t-Tau] or t-Tau/$Aβ_{1-42}$ ratio).*

CSF AD biomarker testing was not used to assess brain Aβ deposition in early stage AD to determine eligibility for the EMERGE/ENGAGE studies of aducanumab; only Aβ PET scanning was utilised. The applicant indicated that Lumipulse kits from Fujireibo was used for the CSF AD biomarker assays in a substudy of EMERGE/ENGAGE. Testing for CSF AD biomarkers is considered by the applicant as an appropriate alternative to Aβ PET for confirming brain Aβ deposition in early stage AD. Studies confirming concordance between Aβ PET and CSF AD biomarker testing and between individual CSF AD biomarker tests were identified in the Application. Concordance between the Aβ PET and CSF biomarker testing increases if the ratio of Aβ 1-42 peptides to tau in CSF is measured.

The Application states that the proposed service can utilise any available CSF AD biomarker assay kit or platform. Immunoassay kits for the assessment of CSF AD biomarker proteins (Aβ 1-42 peptide,

total tau, and phosphorylated tau) are approved and commercially available outside of Australia. There are currently two TGA approved and National Association of Testing Authorities (NATA)/International Laboratory Accreditation Cooperation (ILAC) accredited immunoassay kits for clinical diagnostic use in Australia, the Fujirebio INNOTEST and the Roche Elecsys CSF AD biomarker assay kits. These commercial kits have been validated against Aβ PET by the manufacturers. The INNOTEST and the Elecsys assays were validated by the National Dementia Diagnostics Laboratory (NDDL) to generate pre-defined cut-offs/thresholds for Aβ positivity and negativity. Only the manufacturers of Elecsys and Lumipulse test kits provide pre-defined cut-offs/thresholds values for Aβ positivity and negativity.

PASC noted that there are two CSF biomarker assay test kits used in Australia – Elecsys (Roche) and INNOTEST (Fujirebio) – which are both listed on the ARTG. The applicant clarified that although both assay kits are TGA registered, their corresponding ARTG numbers are not yet published on the ARTG register. Confirmation of the registrations will have to be made available for the assessment phase.

At the April 2021 PASC meeting, the applicant advised the Florey National Dementia Diagnostics Lab (NDLL) is the only laboratory providing a CSF biomarker service and it is only using the Elecsys assay kits.

PASC noted three analytes are included in the CSF biomarker test, however it remained unclear how many of these analytes would be used. PASC advised that the analyte thresholds for Aβ positivity (quantities and/or ratios) will also need to be defined in order to establish the concordance of the nominated CSF biomarker test options and the Aβ PET scan. Additionally, it was agreed that related CSF biomarker thresholds for establishing aducanumab eligibility would have to be included and assessed in the assessment report, recognising such thresholds would be relevant for inclusion in the PBS restriction (and possibly the explanatory notes of the MBS item) rather than the MBS item descriptor.

It would be expected that, in line with other *in vitro* diagnostic assay kits for targeted therapies, pathologist training and a quality assurance program for the use of CSF AD biomarker testing 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.

The Application claims that the availability of CSF AD biomarker testing on the MBS in addition to Aβ PET would improve accessibility to testing for patients in regions of Australia with limited access to PET scanning facilities and offer increased testing capacity. However, discussions with clinical specialists suggest that use of lumbar puncture is not widespread or available in some specialist clinics in Australia and may not be as acceptable to patients as non-invasive PET scanning.

PASC noted the applicant's claim that obtaining CSF samples for biomarker testing is more widely accessible than Aβ PET and therefore CSF biomarker testing should be allowed as an alternative for Aβ PET scanning. However, PASC noted that, for the Florey NDDL, which is the only laboratory that currently performs CSF biomarker testing, strict processing, storage and transport criteria apply to the CSF samples before they can be analysed.

Clinical setting of tests

The proposed services would only be ordered by a specialist clinician experienced in the diagnosis and management of patients with AD. They would not be ordered by GPs.

Aβ PET could be provided in both inpatient and outpatient settings. Consistent with other PET services rebated on the MBS, Aβ PET examinations would only be performed by, or under the supervision of, a registered nuclear medicine specialist.

For CSF AD biomarker testing, CSF collection by lumbar puncture and some pre-analytical handling of the specimen could take place in both inpatient and outpatient settings. A certified pathologist is usually responsible for overseeing CSF AD biomarker testing and reporting of results. It is proposed by the applicant that CSF AD biomarker testing would be undertaken in NATA accredited pathology laboratories.

PASC noted that CSF AD biomarker testing was described as requiring a CSF sample obtained by lumbar puncture and that this would be covered by MBS item 39000. However, PASC advised that MBS item 23010 cannot be billed in this setting, and that hospital admission (day hospital or other) should usually not be needed. PASC further noted that the use of an image intensifier or a CT scanner may be required to guide the lumbar puncture procedure. Given a lumbar puncture for this purpose would be performed in a generally older cohort of patients, PASC considered that image guidance with fluoroscopy or CT would be used frequently in this setting, noting separate MBS items are available for this.

Test timing

It is anticipated that patients will be referred for either Aβ PET or CSF AD biomarker testing after referral to a specialist service, memory clinic, or specialist clinician experienced in the diagnosis and management of patients with cognitive impairment disorders or dementia, including AD. When a specialist has made a diagnosis of possible or probable early stage AD (MCI due to AD/prodromal AD or mild AD dementia) and other causes of the MCI or mild dementia have been ruled out, patients would be considered eligible for the proposed codependent tests.

Testing 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.

Patients who initially test negative may be tested again on follow up if no other underlying cause for their cognitive impairment can be ascertained. There was no suggestion by the applicant as to what window would be considered as reasonable for retesting someone with a negative test result.

Rationale

Aβ PET was used to confirm presence of brain Aβ deposition and hence determine eligibility for the Phase III studies EMERGE/ENGAGE. The Aβ PET test and the circumstances of testing (including the tracers and centralised visual read) used in the key studies is regarded as the evidentiary standard for the purposes of this assessment. Multiple comparisons will be required to confirm the clinical

utility and validity of the two test options proposed for use in Australia. The extent of positive and negative disconcordance of the two testing options will be assessed against the evidentiary standard above. For Aβ PET, this comparison will apply to all individual radiopharmaceuticals available for use in Australia. Similarly, commercially available CSF AD biomarker assays available in Australia will be compared to the evidentiary standard above and the CSF AD biomarker assay used in EMERGE/ENGAGE. Concordance between CSF AD biomarker assays will also be evaluated. Finally, concordance between Aβ PET and CSF AD biomarkers assays available in Australia will be determined.

Aβ PET scanning may have additional utility for tested patients and their carers/family by supporting an AD diagnosis. The applicant acknowledged that results of these tests may have additional clinical utility in AD patients beyond eligibility for aducanumab treatment. Should the proposed MBS items become "uncoupled" from aducanumab codependent treatment, the classification of Aβ PET as the evidentiary standard would no longer be relevant and the accuracy of Aβ PET and CSF AD biomarker testing in confirming a diagnosis of early stage AD would have to be assessed on their own merit. Aβ PET scanning cannot be used alone to establish diagnosis of AD due to increased Aβ deposition with age (>75 years) that may occur in the absence of confirmed AD dementia.

The proposed testing frequency is once per lifetime. Whether there is a requirement for sequential use of the tests or retesting using the same test due to equivocal findings is unclear. The assessment should seek to address the circumstances under which more than one test (either repeat testing or sequential testing with different test modalities) may be required, and the implications of restricting the test to once per lifetime.

If there are reasons for requiring access to either of the tests more than once per lifetime, the expected yield and additional resource use should be presented as supplementary clinical, economic and financial analyses.

Repeat testing

PASC agreed with the proposal that the item descriptors for the two test options should not allow a test to be billed to Medicare if Medicare has already been billed for the alternative test for the requested purpose of determining eligibility for aducanumab.

Acknowledging that a proposed once per lifetime limit for each of these two test options was too restrictive, PASC advised that the circumstances in which either test option could be repeated for other purposes (and the appropriate time interval before repeating the test for the purpose determining eligibility to aducanumab) need to be further clarified, such as:

- *whether to re-test a patient with a previous negative result;*
- *if sufficient evidence were to be adduced for the use of either Aβ amyloid PET or CSF biomarker testing as surrogate outcomes for treatment effectiveness, whether to re-test a patient to assess the patient for any amyloid response (for example in the context of any proposed continuation restriction for aducanumab on the PBS) and/or undertake any other treatment monitoring.*

Evidence justifying re-testing will also need to justify any recommended test/re-test interval.

Codependent treatment

Aducanumab is a human, anti-Aβ immunoglobulin G1 monoclonal antibody that selectively binds to Aβ fibrils and soluble oligomers reducing the amount of Aβ, including the number of amyloid plaques, present in the brain. It is proposed that this may slow neurodegeneration and reduce disease progression. Patients fulfilling clinical criteria for early stage AD and confirmed as positive for brain Aβ deposition, based on the codependent test result, would be eligible for treatment with aducanumab.

Aducanumab would be administered via intravenous infusion once every 28 days. The intravenous infusion takes up to 1 hour. The Department confirmed that a new MBS item is not required for intravenous infusion of aducanumab; this service should be included as part of a consultation with a specialist.

Aducanumab will be initiated at a dose of 1mg/kg, with escalation to 3mg/kg, 6mg/kg, and 10mg/kg doses. Aducanumab efficacy has been demonstrated in EMERGE/ENGAGE for a 10mg/kg dose. Gradual drug dose escalation is required following treatment initiation to reduce the incidence of both amyloid-related imaging abnormality-(o)edema (ARIA-E) and amyloid-related imaging abnormality-haemorrhage (ARIA-H). Both ARIA-E and ARIA-H have been observed in clinical studies of amyloid-modifying treatments including aducanumab. The MRI signal changes in the brain observed in ARIA-E are thought to represent vasogenic oedema, while those observed in ARIA-H range from haemosiderin deposits to microhaemorrhages and macrohaemorrhages. Potential risk factors for development of ARIA include age, drug dose, and ApoE4 status (Sperling et al. 2011). ARIA-E and ARIA-H are often asymptomatic as observed for aducanumab in EMERGE/ENGAGE and only evident on MRI. MRI was used in EMERGE/ENGAGE to monitor development of ARIA; whether or not MRI monitoring will be necessary with the use of aducanumab in clinical practice will not be known until after any TGA registration for aducanumab is finalised. When present, symptoms of ARIA are often transient but can be severe in some cases. Presence of ARIA-E or ARIA-H may lead to either temporary or permanent discontinuation of aducanumab treatment. Dose escalation to the original dose may be required when treatment is restarted.

PASC noted aducanumab is to be administered as a 1 hour IV infusion every four weeks. PASC noted the infusion is not claimable under the currently available MBS items 13950 or 14245 as these are chemotherapy-specific items. PASC noted that monitoring for amyloid-related imaging abnormalities (ARIA-E [(o)edema] and ARIA-H [haemorrhage]) requires one or more MRI scans and that the applicant suggested an additional MBS item be made available for this purpose with a fee of $403.20 should such monitoring be mandated by the TGA.

PASC queried how, if either or both tests are recommended for listing, they could be restricted to aducanumab treatment, and why these tests would not be available to the entire mild cognitive impairment / mild dementia population?

Comparators

The nominated comparator for both proposed testing options is "No testing for Aβ deposition". An additional comparator for Aβ PET is FDG PET. At the time of PASC's first consideration in December 2020, it was noted that the outcome of Application 1195.1 considered by MSAC at its November 2020 meeting, requesting MBS listing of FDG PET to establish a diagnosis of AD where other diagnostic methods are inconclusive, was not yet available. PASC considered that if MSAC was to support Application 1195.1, then it would be an appropriate additional comparator for Aβ PET.

PASC noted the applicant's pre-PASC comment that FDG PET is not a relevant supplementary comparator as it is used for confirmation of a clinical diagnosis of AD if current methods are inconclusive. Further, the applicant stated that, even if FDG PET was conclusive in diagnosing AD, Aβ PET would still be required to determine eligibility for aducanumab. The applicant acknowledged that FDG PET could be considered a comparator for reaching a diagnosis if AD, if a clinician chose to perform Aβ PET scan rather than an FDG PET scan in a patient with MCI.

Following the December 2020 PASC meeting, the MSAC's support of Application 1195.1 was made publicly available. Subsequently, the applicant agreed that FDG PET was a relevant supplementary comparator for Aβ PET scanning. It was clarified that FDG PET would not be considered as an alternative test for the purpose of accessing aducanumab on the PBS. Rather, the comparison to be presented in the assessment report would be a scenario analysis, to assist MSAC in determining the cost-effectiveness of Aβ PET scanning compared to the currently available testing options.

PASC noted that at its November 2020 meeting, MSAC supported the creation of a new MBS item for FDG PET for the diagnosis of AD where clinical evaluation is inconclusive.

PASC noted that in its April 2021 pre-PASC response, the applicant agreed that FDG PET scanning was a relevant supplementary comparator to Aβ PET scanning. PASC confirmed that FDG PET is a relevant supplementary comparator, relevant for assisting MSAC in determining the cost-effectiveness of Aβ PET scanning compared to the current available testing options, and is not an alternative test for the purpose of accessing aducanumab.

The additional comparator for CSF AD biomarker testing is Aβ PET.

The evidentiary standard for both proposed tests is Aβ PET scanning to confirm Aβ pathology conducted as per screening for inclusion in the aducanumab Phase III studies EMERGE/ENGAGE. The evidentiary standard includes the circumstances of testing including the particular radiopharmaceuticals and the criteria for eligibility (centralised visual read) as applied in these studies. The extent of positive and negative disc concordance of the proposed services as conducted in Australia will be assessed against the evidentiary standard.

The relevant comparator for the codependent drug is accepted standard of care (SoC), which depends on the category of early stage AD of the patient. For patients with a clinical diagnosis of MCI with AD/prodromal AD, the relevant SoC is observation and non-drug interventions (optimising brain health, e.g. through activity, cognitive training, and diet). For patients with mild AD dementia, patients can receive treatment with AChEI therapy, e.g., donepezil, galantamine, or rivastigmine, to reduce AD symptoms. All these drugs have TGA approval for use in patients with mild AD dementia and are subsidised through the PBS and Repatriation Pharmaceutical Benefits Scheme (RPBS).

Rationale

The control arm of EMERGE/ENGAGE included patients who had brain Aβ deposition confirmed by Aβ PET scan, and had received SoC according to stage of AD following a clinical diagnosis. As two proposed testing options for Aβ deposition in the brain are available to determine eligibility for aducanumab treatment, these tests will also be compared to each other.

PASC advised that the comparators for Aβ PET scan should be:

- *no testing*
- *FDG PET.*

PASC advised that the comparators for CSF biomarkers should be:

- *no testing*
- *Aβ PET scanning.*

The applicant considered that MRI is not an appropriate comparator as it is not specific to diagnosis AD, noting that in younger patients, hippocampal atrophy is rarely seen in those with positive Aβ scans. The applicant clarified that MRI is used to look for other structural abnormalities as a means of excluding other diagnoses which mimic AD rather than being sufficient to diagnose AD. PASC agreed that MRI is not specific for AD and should not be used as a comparator.

The evidentiary standard for assessment of clinical utility and validity will be Aβ PET as conducted in the Phase III studies EMERGE/ENGAGE to determine eligibility for study inclusion and consequently aducanumab treatment.

PASC advised that autopsy is not the evidentiary standard; rather, it is a reference standard.

PASC advised that the evidentiary standard should include any of the FDA-approved radiopharmaceuticals used in the EMERGE/ENGAGE trial (^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben), with centralised binary (positive/negative) visual assessment. PASC noted that ^{18}F-flutafuranol positivity had not been used as an entry criterion in the aducanumab trials: the diagnostic performance of this agent should be evaluated against the former three.

The SoC in EMERGE/ENGAGE was partially consistent with that described above. Concomitant use of medication for AD symptoms is consistent with permitted use in the EMERGE/ENGAGE study protocols. In EMERGE/ENGAGE, approximately 50% of participants in the treatment arm continued to receive their existing AD medication in addition to aducanumab. Advice received from specialists in dementia indicates that patients testing positive for brain Aβ deposition and receiving aducanumab, would continue to receive SoC (e.g. AChEI therapy). Aducanumab is therefore an additive treatment. However, if patients with MCI due to AD/prodromal AD received AChEI therapy in the study, this would not be consistent with the AChEI PBS restrictions.

Outcomes

The evidence summary in the Application identified published evidence to support the clinical validity and utility of the proposed testing options. The relevant evidentiary standard for the proposed tests is Aβ PET as carried out to determine Aβ deposition in the brain in the Phase III studies EMERGE/ENGAGE.

Direct evidence is available for the codependent drug aducanumab which includes a Phase Ib and two Phase III randomised controlled trials. The Phase Ib study (PRIME) assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab. Interim data from the Phase Ib study was published in 2016. The applicant stated that the codependent submission to MSAC/PBAC will be based on evidence from the Phase III studies (EMERGE and ENGAGE).

The following outcomes are relevant to clinical claims for the proposed tests and codependent treatment.

<u>Patient-relevant</u>

Testing

- Test-related AEs including radiation dosimetry and lumbar puncture
- Psychological and physical harms of Aβ PET and CSF AD biomarker testing results
- Yield of testing
- Change in clinical management

Treatment

- Adverse events related to a change in treatment including tolerability and toxicity.
- Incidence of treatment-related amyloid-related imaging abnormality-(o)edema (ARIA-E) and amyloid-related imaging abnormality-haemorrhage (ARIA-H) events
- Directly measured primary effectiveness outcomes (cognitive, behavioural, and functional impairment, both as an absolute measure and as the rate of decline over time)
- Secondary effectiveness (treatment response rate; duration of treatment response; mortality; rate of hospitalisation; health-related quality of life; change in patient /caregiver reported outcomes; time to admission to full-time care)

<u>Healthcare system</u>

Cost-effectiveness

- Incremental and relative cost-effectiveness of the two proposed testing options for identifying patients eligible for codependent treatment
- Incremental cost-effectiveness of Aβ testing using the proposed test options and aducanumab treatment plus SoC compared to no Aβ testing using the proposed test options and SoC (with and without indirect costs)

Utilisation

- Number of patients tested
- Number of patients treated
- Number of patients tested per Aβ positive result

- Number of patients tested per Aβ positive result treated with aducanumab
- Net overall healthcare costs
- Net cost to MBS
- Net cost to PBS

Other test-related outcomes that may be required are:

Aβ PET

- Accuracy of Aβ PET as conducted via a centralised visual read in EMERGE/ENGAGE (evidentiary standard) against a relevant reference standard – where possible, autopsy within 1 – 2 years of Aβ PET scan
- Analytical performance of Aβ PET as carried out by appropriately trained readers in Australia (extent of positive and negative discordance) in comparison to the evidentiary standard
- Concordance between different Aβ PET radiopharmaceuticals available in Australia

CSF AD biomarker test

- Analytical performance of CSF AD biomarker testing as conducted in Australia (extent of positive and negative discordance) in comparison to the evidentiary standard
- Analytical performance of CSF biomarker testing as conducted in Australia (extent of positive and negative discordance) in comparison to CSF AD biomarker assay used in EMERGE/ENGAGE
- Concordance between different CSF AD biomarker tests conducted in Australia
- Concordance between CSF AD biomarker tests and Aβ PET conducted in Australia

For Aβ PET and CSF AD biomarker tests:

- Test reliability/validity
- Testing yield

Rationale

Additional outcomes to those proposed in the Application have been identified during preparation of the PICO as potentially relevant to testing for Aβ and treatment with the codependent drug.

PASC supported the applicant's proposal to explore whether outcome data comparing the analytical performance of the reads of Aβ PET scans from the EMERGE/ENGAGE trial by readers in the centralised facility for the trial and subsequently by Australian readers following their completion of an authorised training module provided by the supplier prior to the radiopharmaceutical being ordered.

<u>Test</u>

For the proposed test options, the potential harms associated with incorrect/inaccurate test results should be assessed. Early stage AD patients with a false negative or positive test result could be exposed to physical or psychological harms associated with change in management.

PASC noted that, in the trials, the image interpretation was centralised, suggesting that it requires a level of expertise to optimise inter-rater reliability.

PASC considered that the analytical concordance between different CSF biomarker assays and their analytical validity against Aβ PET will require evaluation.

PASC noted that none of the Cochrane reviews of Aβ PET or CSF biomarkers unequivocally recommend the routine use of these technologies.

PASC requested that the safety consequences of radiation dosimetry and lumbar puncture be added to the safety outcomes of Aβ PET and CSF biomarker testing, respectively. Similarly, the cost-effectiveness/cost-utility of Aβ PET and CSF biomarkers should be assessed, including a comparison of these alternatives.

Treatment

The outcomes proposed by the applicant for codependent drug efficacy are based on the aducanumab clinical studies. These outcomes are as recommended by FDA and EMA guidance documents on the conduct of clinical studies in early stage AD. The primary effectiveness outcomes are change in cognitive, behavioural, and functional impairment as assessed by instruments used in clinical studies of aducanumab. These would be assessed as both the absolute change and rate of decline over time. Use of rate of cognitive decline as an outcome reflects that cognitive improvements in patients with AD is unlikely, but rather that the progression rate of impairment may slow due to early identification and treatment. Ability to perform tasks for daily living was assessed during EMERGE/ENGAGE.

PASC considered minimally clinically important difference (MCID) thresholds should be specified for changes in the cognitive, behavioural and functional scales used to evaluate clinical responses to aducanumab, as well as their rates of change.

Response rate and duration of response for patients receiving aducanumab are relevant outcomes for assessment to determine the proportion of eligible patients likely to benefit significantly from treatment and the estimated treatment duration based on benefit.

PASC noted that the applicant suggested removing "response rate" from the outcomes as the aducanumab trials did not define a response and that the objective of treatment with aducanumab was to delay disease progression, rather than elicit a response from patients. This would also affect the proposed outcome of "duration of treatment response". PASC considered that delayed disease progression and different rates of change could be classified as a treatment response, and so requested that the basis for concluding that any particular outcome measure represents a clinically meaningful benefit (for example, via an MCID) would be necessary for the MSAC assessment.

It may not be possible to determine the impact of aducanumab treatment on mortality at this stage, as direct evidence may be limited. The ability to remain independent and avoid admission to full-time care are assessments that reflect AD dementia progression and likely impact on both patient and caregiver quality of life. Measures of HRQoL and patient /caregiver reported outcomes are also relevant to determine the impact of treatment.

"Changes in AD biomarkers" were nominated as a treatment outcome in the Application. These are unproven surrogate outcomes for patient-relevant health outcomes, such as cognitive impairment

or mortality. Validation requires evidence that Aβ PET or CSF AD biomarker testing detects changes in Aβ deposition in the brain that correlate with changes in patient-relevant outcomes, such as cognition, behaviour or functioning. Changes in clinical outcomes (cognitive or functional performance) did not correlate reductions in PET or CSF amyloid markers in the aducanumab Phase III sub-studies. A statement by the applicant's representative that changes in clinical outcomes may lag behind changes in marker levels is not substantiated by any evidence provided to date.

PASC advised that using 'changes in AD biomarkers' after treatment with aducanumab treatment was not a suitable treatment outcome, as a change in an AD biomarker is an unproven surrogate outcome for patient-relevant health outcomes, such as cognitive impairment or mortality.

PASC noted three clinical trials were referenced by the applicant. These were the Phase Ib PRIME trial and two Phase III studies, ENGAGE and EMERGE. PASC noted that none of the aducanumab clinical trials have been published.

PASC noted that, within the two phase III studies, sub-studies looked at Aβ PET, CSF biomarker and tau PET changes. PASC noted the Aβ PET substudy reported a dose-response relationship between the dose of aducanumab administered and the amount of Aβ in the brain as detected by the Aβ PET scan in both the EMERGE and ENGAGE studies over a 78 week period. Although changes in CSF biomarkers were observed in the CSF biomarker substudy across both the EMERGE and ENGAGE studies, they only appeared to be dose-related in the EMERGE study. However, only a barely statistically significant difference in the primary clinical endpoint was demonstrated in the high-dose group in the EMERGE study, with no difference demonstrated in the identically performed ENGAGE study. PASC noted there was no obvious correlation between a change in these biomarkers and clinical progression, therefore PASC considered these biomarkers should not be used as a measure of disease progression. The applicant disagreed, noting there is evidence to support a correlation between a reduction in amyloid burden and a change in primary and secondary clinical endpoints in the trials, which will be provided in the evaluation phase for both PBAC and MSAC consideration.

Impact on healthcare system

These tests are presented in the Application as alternative options for determining eligibility for aducanumab treatment by confirming the presence of the drug target, Aβ deposition in the brain. They are not proposed in the Application for utilisation as AD diagnostic tests. It is anticipated that only one of the two test options would be carried out per patient at a frequency of once per lifetime. The proposed MBS items state that these tests will be requested by a specialist clinician experienced in AD dementia. Assessment prior to requesting the tests will not impact on healthcare resources as these are already part of the current clinical management algorithm used in Australia. The applicant provided an estimate of proposed service utilisation for Australia based on one test per eligible patient and anticipated uptake by early stage AD patients. It is estimated that approximately **REDACTED** early stage AD patients would access these services in the first year (**REDACTED** for Aβ PET and **REDACTED** for CSF AD biomarker testing) to determine eligibility for treatment with the codependent drug. In the subsequent two years, a similar number of early stage AD patients would be expected to access these services each year (**REDACTED** patients in year 2, **REDACTED** patients in year 3) (see Table 6; page 13 of the Application form).

Aβ PET is currently not available on the MBS. If Aβ PET scanning is listed as a codependent service, demand for access to PET scanning will increase. An Aβ PET scan requires a CT scan for attenuation correction purposes which can be carried out under MBS Item 61505 as of May 2020. Consumables required for Aβ PET scanning are radiopharmaceuticals which are administered by intravenous injection. The Aβ PET scanning can be carried out on an in-patient or out-patient basis. Qualitative binary assessment of an Aβ PET scan as positive or negative for brain amyloid must be done by an expert reader who has completed appropriate training with the radiopharmaceutical manufacturer. The applicant indicated that quantitative standardisation using SUVR or Centiloid values may be requested as part of the scanning service.

The CSF AD biomarker testing requires a CSF sample obtained by lumbar puncture which can be carried out in an out-patient clinic with the subsequent sample processing and testing conducted in an accredited pathology laboratory. Consumables required are commercial immunoassay kits and reagents. Lumbar puncture would be covered by MBS item 39000 either with or without anaesthesia (MBS item23010). Use of an image intensifier or a CT scanner may be required to guide the lumbar puncture for which separate MBS items are available.

MRI may be required to confirm presence of ARIA-E and ARIA-H events associated with aducanumab treatment. These events were observed in ~40% of patients during EMERGE/ENGAGE receiving the highest 10mg/kg dose of aducanumab. As this is the aducanumab dose with treatment efficacy, similar events are likely to occur during clinical use. *PASC also noted aducanumab treatment was associated with a significantly higher incidence of falls and shorter time to first fall in the high-dose population, which it considered to be an important outcome, particularly in this population which tends to be more elderly. Similarly, PASC added treatment-related ARIA-E and ARIA-H events to the safety outcomes, and rates of hospitalisation to the effectiveness/healthcare system outcomes.*

There is uncertainty regarding the need for MRI monitoring of ARIA at the current time as aducanumab is yet to undergo assessment by the TGA. In line with advice provided by the Department, a new MBS item is requested for this purpose. This request may be withdrawn if monitoring by MRI is subsequently not required/mandated. A draft of the proposed MBS item descriptor for MRI monitoring of ARIA is provided below in the "Proposed item descriptors" section.

Current MBS items for MRI include restrictions on reimbursement based on maximum number of MRI scans per annum per anatomical location (e.g. brain). The draft MBS item descriptor for MRI monitoring of ARIA limits the number of MRI scans to three per year based on frequency of monitoring assessments described in the EMERGE/ENGAGE study protocols, but this frequency restriction should be discussed with the applicant.

Potential improvements in a patient's health outcomes may impact positively on their carers' and family members. Indirect benefits (ability to continue working and maintain social life) may be relevant to explore in a supplementary analysis.

<u>Additional relevant outcomes for assessment</u>

The extent of positive and negative discordance of all possible test options (non-centralised visual reads and CSF AD biomarker immunoassay kits) will be determined by comparison to the evidentiary

standard. There are currently two TGA-approved commercial AD biomarker kits, INNOTEST (Fujirebio/Asquith Diagnostics) and Elecsys® (Roche Diagnostics).

As CSF AD biomarker testing was not used to determine eligibility for inclusion in the EMERGE/ENGAGE studies, an assessment of the extent of positive and negative discordance between Aβ PET and CSF AD biomarker testing is needed for determining a positive or negative result for brain Aβ deposition in early stage AD. Both tests should be identifying the same patient population as being eligible for aducanumab treatment. The applicant indicated that "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" suggesting that direct evidence for discordance may be supplied in the ADAR.

Concordance of Aβ PET carried out across radiopharmaceuticals available in Australia (^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben, and ^{18}F-flutafuranol) for identifying Aβ deposition in early stage AD will be evaluated. The applicant indicated that the proposed service "can utilise any available radiopharmaceutical and does not specify use of any one particular Aβ PET radiopharmaceutical".

As the applicant acknowledged that the proposed tests may have additional clinical utility beyond eligibility of aducanumab (e.g. AD diagnosis or prognosis), the ethics of testing and impact on value of knowing will need to be explored. However, it is acknowledged that these outcomes are not integral to the purpose of the tests for the codependent submission.

Current clinical management algorithm for identified population

In the current management algorithm included in the Application, a patient would become eligible for the proposed tests at the point at which a specialist confirms a clinical diagnosis of early stage AD (blue boxes). The applicant included FDG PET in the clinical management algorithm as an alternative option to SPECT; FDG PET is not currently MBS funded for this purpose but may be available in the event that the November 2020 MSAC meeting supports Application 1195.1. It is possible that patients with an "inconclusive or negative" diagnosis may require further specialist assessment and/or SPECT/FDG PET (if available) which needs to be reflected in the algorithm by addition of an arrow back to this box.

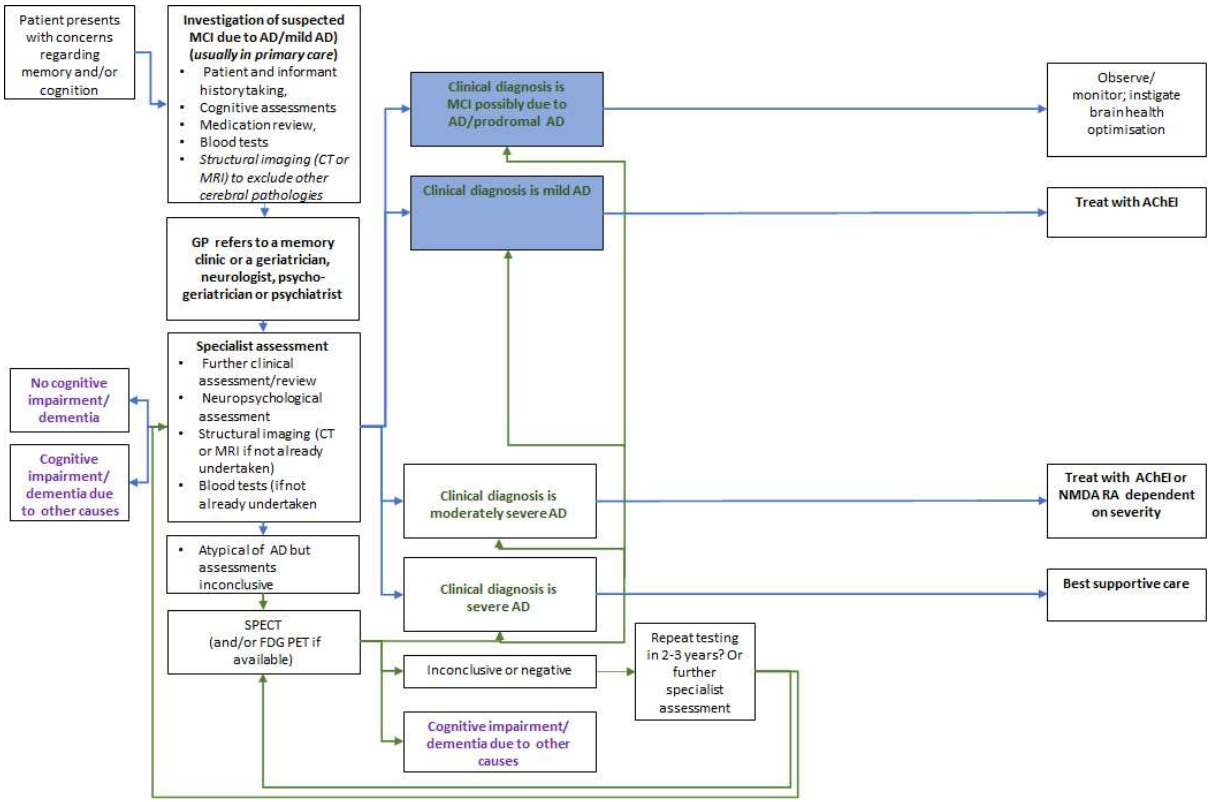

Figure 1: current clinical management algorithm

AChEI, acetylcholine esterase inhibitor therapy, e.g., donepezil; AD, Alzheimer's disease; CT, computerised tomography; FDG PET, fluorodeoxyglucose positron emission tomography (not currently reimbursed on the MBS); MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NMDA RA, N-methyl-D-aspartate receptor antagonist therapy, e.g. memantine, SPECT, single-photon emission computerized tomography;

Proposed clinical management algorithm for identified population

Patients with a clinical diagnosis of early stage AD , that is, MCI possibly due to AD/prodromal AD or mild AD who are found to be positive for brain Aβ using either Aβ PET or CSF AD biomarker testing would be able to access aducanumab treatment via the PBS. The option "treat with aducanumab" in the red boxes should be "treat with aducanumab + SoC", as discussed previously. The red boxes with "investigate alternative causes of cognitive impairment" should have red arrows back to the black box for "specialist assessment" to reflect the need for further specialist investigation if their test is negative for brain Aβ deposition. Further assessment may also include SPECT, or FDG PET if available as discussed above. If monitoring of ARIA during aducanumab treatment is recommended or required, as discussed above, then this should be added to the proposed algorithm.

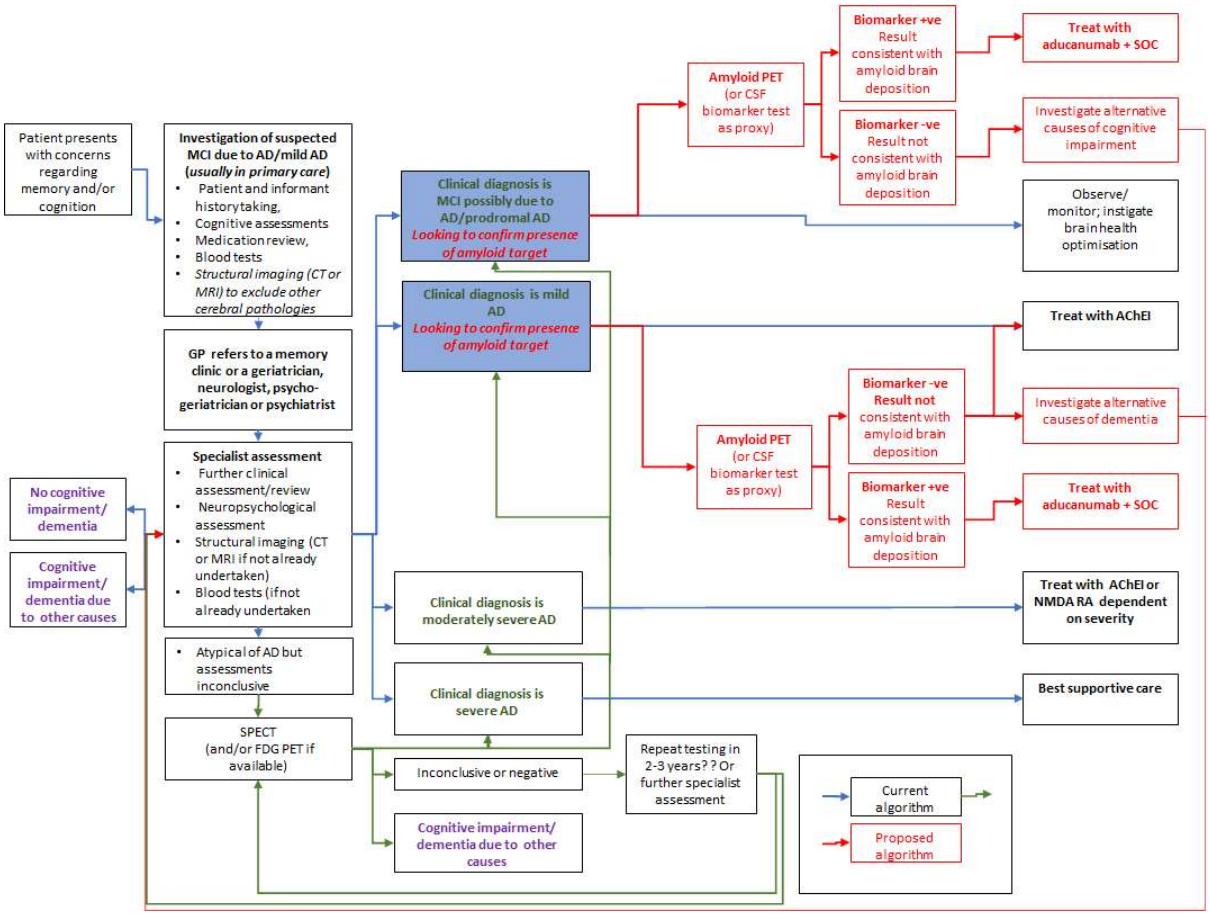

Figure 2: Proposed clinical management algorithm

AChEI, acetylcholine esterase inhibitor therapy, e.g., donepezil; AD Alzheimer's disease; CDAMS, Cognitive Dementia and memory Service (Victoria); CT, computerised tomography; FDG PET, fluorodeoxyglucose positron emission tomography (not currently reimbursed on the MBS); MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NMDA RA, N-methyl-D-aspartate receptor antagonist therapy, e.g. memantine, SPECT, single-photon emission computerized tomography

PASC noted that the referral pattern for the proposed clinical management algorithm is the same for the current clinical management algorithm. In the proposed clinical management algorithm, the patient will then go on to Aβ PET scan or CSF biomarker testing if diagnosed with MCI or mild AD. If the result (Aβ PET or CSF biomarker) is positive, the patient will go on to be treated with aducanumab, otherwise if the result is negative, the clinician will seek alternative causes of dementia other than AD.

PASC agreed with the additions made by the applicant to the current proposed clinical management algorithm in its pre-PASC comments, making it possible for the test to be repeated. However, consistent with its earlier advice, the following issues need to be accurately reflected in the assessment report algorithms:

- *the role of FDG PET as a comparator rather than a prior test*
- *the justification for (and timing of) subsequent Aβ PET or CSF biomarker testing in the proposed clinical management algorithm.*

The applicant reiterated its intention to discuss the role of FDG PET in a presubmission meeting with the MSAC Secretariat.

Proposed economic evaluation

The applicant considered that direct evidence presented in the ADAR will support its claim that Aβ testing followed by aducanumab treatment is superior to no Aβ testing and current SoC for patients with early stage AD. Use of FDG PET may be included in the model if approved by MSAC for listing on the MBS.

If evidence in the evaluation confirms that safety and/or effectiveness is superior, then a cost-effectiveness or cost-utility analysis would be appropriate.

PASC noted that the Application's claim that Aβ testing (with either Aβ PET or CSF biomarker levels) followed by aducanumab treatment, in addition to SoC, is superior to no Aβ testing and current SoC for patients with early stage AD. On this basis, PASC agreed that the economic evaluation to be presented in the assessment phase should be a cost-effectiveness or cost-utility analysis.

To assess the comparison with FDG PET, the economic evaluation should present a scenario analysis to enable the justification of any fee differential across FDG PET and Aβ PET should that emerge.

Proposed item descriptors

The MBS item descriptors for Aβ PET and CSF biomarker testing proposed for PASC's consideration are provided below:

Category 5 – DIAGNOSTIC IMAGING SERVICES Beta-amyloid positron emission tomography (PET) study of the brain, with or without quantitative assessment, performed once per lifetime for the evaluation of a patient with a clinical diagnosis of early stage Alzheimer's 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: $918 Benefit: 75% = $#### 85% = $###
Category 6 - PATHOLOGY SERVICES Quantification, by immunoassay methodology performed once per lifetime, of amyloid and tau proteins in cerebrospinal fluid from a patient with a clinical diagnosis of early stage Alzheimer's disease, requested by the specialist or consultant physician 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: $250 Benefit: 75% = $#### 85% = $###

The revised MBS item descriptors for Aβ PET and CSF biomarker testing p following the April 2021 PASC meeting are provided below (noting PASC considered further amendments were required):

Category 5 – DIAGNOSTIC IMAGING SERVICES
Beta-amyloid positron emission tomography (PET) study of the brain, with or without quantitative assessment, for the evaluation of a patient with a clinical diagnosis of early stage Alzheimer's disease, requested by the specialist or consultant physician, to determine if the requirements relating to the amyloid status for access to 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: $918 Benefit: 75% = $#### 85% = $###
Category 6 - PATHOLOGY SERVICES
Quantification, by immunoassay methodology of amyloid and tau proteins in cerebrospinal fluid from a patient with a clinical diagnosis of early stage Alzheimer's disease, requested by the specialist or consultant physician, to determine if the requirements relating to the amyloid status for access to 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: $300 Benefit: 75% = $#### 85% = $###

The proposed population in both MBS item descriptors is "patient with a clinical diagnosis of early stage Alzheimer disease". The applicant proposed that that the target patient population be referred to as "early stage AD" for the purposes of the PICO Confirmation as the proposed indication for aducanumab is not yet finalised by the TGA. Efficacy of aducanumab has been demonstrated in the Phase III studies EMERGE/ENGAGE in patients with early stage AD but this patient population is more specifically defined by the Phase III study inclusion criteria as patients with MCI due to AD/prodromal AD or mild AD dementia, according to the NIA-AA and IWG guidelines. Direct evidence of efficacy outside these populations has not been provided in the Application. *PASC advised that "early stage Alzheimer's disease" should be defined in an explanatory note.*

The descriptors proposed by the applicant did not include a statement limiting the use to one test option only and once per lifetime for the purpose of determining eligibility for aducanumab. This restriction on test frequency remains an uncertainty to be addressed during the assessment report. The restriction of once per lifetime was added to the descriptor for each test for consideration by PASC.

As noted in the Intervention section above, PASC considered the restriction of "once per lifetime" to be too stringent. However, the justification for, and frequency of, repeat testing would need to be established from evidence presented in the Assessment Report, as well as the sequencing of the tests and whether they are confirmatory.

The applicant agreed with PASC that one test per lifetime is likely to be too restrictive and undertook to identify evidence which may justify repeat testing in clinically relevant circumstances.

At its April 2021 meeting PASC reinforced its previous advice that a repeat test should only be made available to account for test failure for a person who tests negative to be retested at a justifiable time point in the future for the purpose of reassessment for access to aducanumab.

PASC advised that "who manages the treatment of the patient" is redundant and can be removed from the proposed item descriptor.

PASC noted the inclusion in the proposed item descriptors of the sentence "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." PASC considered that, to make this meaningful to requesters and providers of the proposed items, these other eligibility criteria should be specified in the MBS item descriptor.

The item descriptors (or their explanatory notes) will need to take account of the following:

1. *Testing (+/- re-testing) using one option (Aβ PET or CSF biomarker) needs to deny reimbursement for the alternative option;*
2. *Testing is limited to consideration for access to aducanumab, and not to the diagnosis of AD more generally. (Implementation of this requirement is likely to be problematic.)*

The total estimated costs associated with the proposed test services are provided in the Application. These are based on assumptions at this stage. The applicant's total estimated cost for Aβ PET using a PET/CT scanner is $1018.00. This is based on estimates used for the FDG PET Application 1195.1 and covering most associated costs including the Aβ PET radiopharmaceutical, PET scan and Aβ PET interpretation. The proposed MBS item fee is $918.00.

PASC noted that the proposed fee of $918 for Aβ PET is based on FDG PET scans for refractory epilepsy. There will be an additional $100 fee for any concurrent CT scan, however any concurrent MRI scan would result in an out-of-pocket cost for the patient.

PASC noted that the proposed fee does not include the cost of the radiopharmaceutical. Consultation feedback indicated that the current typical cost per radiopharmaceutical dose is $1200, and the product is shipped from Melbourne with a $400 delivery fee. PASC considered that this proposed fee would therefore likely result in a substantial out-of-pocket cost for the patient if not included in the MBS fee.

The total estimated cost of CSF AD biomarker testing is $997.10. This includes lumbar puncture (reimbursed on the MBS item numbers 21945, 39000), day private hospital admission (if necessary) for the performance of lumbar puncture (includes costs of use of fluoroscopic or CT guided procedure) and the CSF test assay. The MBS policy unit have advised that MBS item number 21945 can be claimed by a non-anaesthetist, but it cannot be claimed by the same practitioner performing the procedure (lumbar puncture). There does not appear to be a separate anaesthetic item available to claim for the practitioner who is also performing the lumbar puncture. The proposed MBS item fee for the CSF test assay is $300.00.

PASC noted that, in the applicant's April 2021 pre-PASC response, the proposed fee for the CSF biomarker assay Elecsys had been revised from $250 to $300, consistent with current charging by the Florey NDDL. PASC noted the proposed fee of $918 for Aβ PET scanning had not been revised since the December 2020 meeting. PASC again raised concern about the potential for out-of-pocket costs for patients, given the cost of the radiopharmaceutical is not included in the proposed fee.

PASC considered that a restriction should be included in the item descriptors to allow only for one of the two proposed test options, Aβ PET scanning or CSF testing, to be reimbursed for the purpose of helping to assess a patient's eligibility for aducanumab.

PASC considered there was a high risk of leakage because Aβ PET scanning may be used for initial diagnosis of AD rather being limited to those patients being considered for aducanumab. Further, PASC noted the Department queried the appropriateness of performing both FDG PET and Aβ PET scans on the same patient and suggested a restriction should be put in place to prevent claiming of both these items for a patient in a 12-month period. PASC considered that this suggestion was not appropriate as both scans had two distinctly different purposes, with FDG PET amongst the options used to confirm a diagnosis of AD, and Aβ PET used to establish eligibility for access to aducanumab.

A draft of the proposed MBS item descriptor for MRI monitoring of ARIA is provided below.

Category 5 – DIAGNOSTIC IMAGING SERVICES
Magnetic resonance imaging (MRI) scan of the head (including MRA, if performed) for patients with Alzheimer's disease, treated with aducanumab, to confirm presence or absence of: i. amyloid-related imaging abnormalities-(o)edema (ARIE-E); and/or ii. amyloid-related imaging abnormalities-haemorrhage (ARIA-H)/superficial siderosis
For any particular patient—applicable not more than three times in a 12 month period
MBS Fee: $403.20 Benefit: 75% = $#### 85% = $###

PASC noted the proposed MBS item as a contingency for the MRI to monitor the presence of ARIA-E and ARIA-H during treatment with aducanumab in the event that the TGA mandates this monitoring of patients.

The applicant noted the proposed MRI ARIA monitoring item is limited to testing three times in a 12-month period and that this may need to be increased pending TGA's advice around monitoring requirements, particularly if this advice includes an increased frequency of scanning of a patient who experienced an ARIA.

PASC noted the applicant's position that monitoring of patient response to aducanumab using Aβ PET scanning was not in scope for the requested service and so use of the scan to monitor for a reduction in Aβ deposition as a result of the drug should be precluded in the item descriptor. PASC also noted the view of its clinical expert that accepting this position would likely result in some patients remaining on aducanumab indefinitely without benefit. PASC advised that evidence to assess whether the extent of a treatment effect observed on Aβ deposition predicts a subsequent extent of treatment effect on outcome measures of AD progression should be included in the assessment report to address this issue further.

Consultation feedback

Three organisations and three individuals provided responses to the consultation. All responses were supportive of the Application. Some responses noted that Aβ PET would provide a more accurate and earlier diagnoses of AD compared to current methods, leading to earlier treatment and possible delay of symptom progression. Two responses considered that follow-up Aβ PET scan should also be considered for monitoring response to therapy.

PASC noted the consultation feedback was supportive of the Application.

PASC noted feedback from professional associations that the MBS item wording should be amyloid tracer agnostic. PASC also noted there was disagreement with the once per lifetime restriction and that this should be deleted from the item descriptor.

PASC noted feedback received from individual specialists noting the CSF biomarker testing is invasive and Aβ PET scanning would be the preferred mechanism for assessing amyloid pathology. Further feedback suggested a follow-up Aβ PET scan should be available to reassess the presence of amyloid after 12 months of initiating treatment and that if all amyloid had been removed, treatment with aducanumab could be ceased.

PASC noted that there was no additional public consultation feedback.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application could proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an integrated codependent submission, encompassing an ADAR (applicant developed assessment report).

Applicant Comments on the Ratified PICO

Consultation feedback

The applicant acknowledges that the cost of the radiopharmaceutical should be included in the MBS item number to ensure equity of access and minimise out of pocket expenses.

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