Appendix A: Summary of international HTA reports review

A literature search for published HTA reports for DMDTs was completed on 21 June 2023. Of the 17 sources of information identified, the most comprehensive reports were published by the Institute for Clinical and Economic Review (ICER) for aducanumab and lecanemab (Lin G et al., 2021, Lin G et al., 2023). Aducanumab was also discussed in the Canadian, Australian and Dutch jurisdictions however, the company withdrew the submission before licensing or reimbursement decisions were made and therefore aducanumab is not available as a treatment option. There was less information available for lecanemab, except for the ICER publication. The EMA discussed lecanemab in May 2023, the minutes from this meeting are not yet publicly available.

ICER's Assessment of Aducanumab

ICER assessed the clinical effectiveness and cost-effectiveness of aducanumab in patients with early AD [defined as mild cognitive impairment (MCI) or mild dementia due to AD] and produced policy recommendations based on this assessment (Institute for Clinical and Economic Review (ICER) 2021; Lin et al. 2021). The cost-effectiveness assessment was carried out using a Markov cohort model, and the description of the decision problem and underlying assumptions and results are presented in Table 1 and Table 2, respectively.

The assessment of treatment effectiveness was based on two identical phase 3 clinical trials, EMERGE and ENGAGE that included patients with early AD randomised to low or high dose aducanumab or placebo. The primary outcome of the trials was change in mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). The exact dose received in the trials was based on the presence or absence of apolipoprotein ε4 (APOE4) which is a genetic marker of AD risk. However, mid-way through the trials, there was a protocol amendment so that the high-dose group was titrated to 10mg/kg whether or not APOE4 was present. The trials were terminated early after a pre-specified interim analysis for futility. Post-hoc analyses were carried out that showed that

while both trials showed aducanumab to effectively reduce amyloid levels there seemed to be a positive treatment effect in EMERGE, while ENGAGE did not detect improvements in CDR-SB with aducanumab relative to placebo. The level of difference in CDR-SB that was considered to be important was not clearly defined. Furthermore, this trend was also seen in assessments of secondary clinical endpoints which showed positive results for aducanumab in EMERGE and negative in ENGAGE.

In terms of safety, the pooled results from both trials showed that 35% of patients experience amyloid-related imaging abnormalities with oedema/effusion (ARIA-E), ARIA-haemorrhage or superficial siderosis (ARIA-H) or both. ARIA can range from being asymptomatic to having severe clinical impacts.

Key areas of clinical uncertainty highlighted in ICER's report.

- **Mixed Results**: The ENGAGE and EMERGE trials, produced mixed results. While data suggested that aducanumab might have a positive impact on cognitive decline in some Alzheimer's patients, the overall findings were not consistent. This raised questions about the drug's efficacy. EMERGE and ENGAGE were terminated after a prespecified interim futility analysis determined that they were unlikely to reach the primary endpoint. Post-hoc analysis used an expanded dataset that included 3 additional months of data collected between the data cutoff for the futility analysis and the termination. The analysis of the larger dataset suggested a favourable treatment effect in the EMERGE trial, which underpinned the manufacturer's application to the FDA.

- **Adverse Events**: The EMERGE and ENGAGE trials reported adverse events (ARIA). Pooled safety data from ENGAGE and EMERGE report that 90.7% of participants receiving aducanumab experienced an adverse event as compared to 86.9% in the placebo arm.

- **Dosing and Treatment Duration**: The dosing regimen in the ENGAGE trial included a higher dose of aducanumab compared to the

EMERGE trial. There are concerns about whether the higher dose was associated with more adverse events and whether the trials were of sufficient duration to determine long-term efficacy and safety.

- **Minimum clinically important difference**: The FDA accepted any statistically significant change in CDR-SB as a clinically meaningful outcome. However, there is a difference of opinion on this point. The absolute difference in CDR-SB of 0.39 points seen in EMERGE, while statistically significant, may or may not be representative of a change in status that is clinically meaningful to patients, caregivers, or clinicians.

- **Lack of Long-Term Data**: Given the relatively short duration of the trials, there were uncertainties about the long-term effects and benefits of aducanumab, especially regarding its ability to slow disease progression.

The manufacturer explored some explanations for the discordant results between the trials and their conclusion was that the protocol amendment allowed more patients in EMERGE than ENGAGE to receive the full high-dose regimen and therefore randomisation did not balance “rapid progressors” in ENGAGE. However, ICER found that alternative explanations may be equally likely, for example, the difference between the trials may be due to chance. Furthermore, it is uncertain whether the benefit seen in ENGAGE is a clinical benefit and the relationship between amyloid clearance and clinical improvement is inconclusive. Given the harms in patients treated with aducanumab and uncertainty about benefits, the **ICER report rates the evidence to be insufficient to conclude clinical benefits**. In terms of cost-effectiveness, the ICER report concluded that the price set by the manufacturer was not in line with its clinical benefits. Furthermore, it outlines that If aducanumab were determined to have no net health benefit, no threshold price could be generated to guide considerations of fair pricing.

Committee discussions and recommendations

The appraisal committee deliberated the comparative effectiveness and value of aducanumab and made policy recommendations for pricing, access and future research. The committee voted unanimously that the evidence is inadequate to demonstrate that aducanumab plus supportive care is superior to supportive care alone. The following discussion points were also part of the deliberation process and voting:

- Discordant results from ENGAGE and EMERGE are a key source of clinical uncertainty
- The relationship between beta amyloid clearance and clinical benefit is yet to be demonstrated.
- There is a high unmet need for a disease modifying treatment for Alzheimer's disease. At the time of writing the ICER report (2021), there were no other available drugs approved for use.
- Aducanumab may have a major negative effect on reducing health inequities because while there is a higher prevalence of AD in Black and Hispanic populations, they were underrepresented in the trials. Furthermore, its IV administration means that patients living in rural areas and their caregivers may need to take time off to travel and receive infusions and may find it more difficult to get a prescription by a specialist.

The key policy recommendations that may be relevant to other settings are:

- Payers should evaluate coverage of aducanumab in the context of the evolving evidence on its benefits and harms. It goes on to outline that the use of amyloid clearance as a surrogate outcome is not adequately justified and that it is not unreasonable for payers to deny coverage

with aducanumab pending additional data. If payers do choose to provide coverage, they should cover diagnostics to identify ARIA.

- It was highlighted that the approval process for aducanumab by the FDA left public confidence shaken, and that the designation of amyloid clearance as a surrogate outcome without providing sufficient evidence to support this has set a precedent. It was recommended that the FDA act immediately to define publicly what degree of amyloid reduction it will consider as a minimum to qualify a drug as “reasonably likely” to lead to clinical benefit.

- It was recommended that the manufacturer accelerate plans for an international phase 3 confirmation trial to collect additional evidence.

- It was recommended that patient organisations work to educate patients about the potential risks and benefits of new treatments, in particular those with the potential for substantial harms. It was also recommended that patient organisations work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. They should also publicly promote access and fair pricing of new therapies.

- It was recommended that drug development be accompanied by robust research into novel diagnostic strategies that have the potential to identify the target population more accurately, and possibly minimise costs and harms to patients.

ICER’s Assessment of Lecanemab

ICER assessed the effectiveness and cost-effectiveness of lecanemab in addition to supportive care, versus supportive care alone in patients with early Alzheimer’s disease (Lin et al., 2023; Institute for Clinical and Economic Review (ICER), 2023). The cost-effectiveness assessment was carried out by adapting the Markov cohort model used for the assessment of aducanumab.

A description of the decision problem and underlying assumptions and results are presented in Table 1 and Table 2, respectively.

The assessment of treatment effectiveness was based on the phase 3 evidence from CLARITY AD which randomised participants with early AD [i.e., mild cognitive impairment (MCI) or mild dementia due to AD] to lecanemab or placebo. The primary outcome in the trial was change in mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) and it lasted 18 months. At the end of the trial, there was a statistically significant slowing in cognitive decline as measured by CDR-SB in the lecanemab group relative to placebo observed. Analyses of secondary endpoints including other cognitive measures and carer's quality of life favoured lecanemab,

In terms of safety, the trial results showed that 21.5% of patients in the lecanemab group experienced amyloid-related imaging abnormalities with oedema/effusion (ARIA-E), ARIA-haemorrhage or superficial siderosis (ARIA-H) or both, while 9.5% of patients in the placebo group experienced it.

The estimated lifetime cost-effectiveness results for lecanemab in addition to supportive care compared to supportive care alone based on the annual price of lecanemab of $26,500 exceeded commonly used cost-effectiveness thresholds in the US. Some key results are presented in Table 2. A discount of 66% to 19% from lecanemab wholesale acquisition cost would be required for it to fall within ICER's Health Benefit Price Benchmark for lecanemab which is $8,900 to $21,500.

Key areas of clinical uncertainty highlighted in ICER's report.

- **Amyloid hypothesis:** It is expected that if the amyloid hypothesis is correct, removal of amyloid should be associated with treatment effect. The data for lecanemab does not demonstrate a correlation between amyloid removal and treatment effect. The pathophysiology of Alzheimer's disease is complex and the role of amyloid and what factors including degree of removal, threshold of removal for treatment

efficacy, or removal of certain amyloid subspecies impact clinical outcomes is unknown.

- **Minimum clinically important difference (MCID):** mean change in an outcome represent population aggregated changes and will obscure changes individual patients that are above or below the MCID. Manufacturers should provide analyses to show the percentage of clinically important decline in the treatment and placebo groups. Group change does not capture patient level change and does not reflect benefit to individuals. Some experts have suggested the MCID for CDR-SB is 1 or 2 points. There is disagreement between experts whether the absolute difference of 0.45 in CDR-SB observed in CLARITY AD reflects a clinically meaningful change.

- **Functional unblinding:** Experts have raised concerns that treatment efficacy in the clinical trials of anti-amyloid therapies may reflect 'functional unblinding'. This is likely to occur when patients and caregiver and providers recognise that patients who develop ARIA are more likely to be on active treatment rather than placebo. To protect against functional unblinding, equal numbers of patients in each treatment arm should be managed as though they had developed ARIA. This was not done in CLARITY AD. ICER reviewed the data to investigate if ARIA frequency correlated with benefit. No evidence of a correlation was found and therefore, it is unlikely the treatment efficacy observed in trials is due to functional unblinding.

- **Adverse effects:** Real- world treatment risk of ARIA is likely to be greater than seen in the trials. Labelling is unlikely to require the intensity of MRI monitoring that was conducted in CLARITY AD.

- **Stopping rule:** It is unknown if treatment should be continued indefinitely or discontinued when a specified degree of amyloid clearance is reached, or at a specific point in the disease course.

The report authors concluded that there is evidence that lecanemab slightly slows down cognitive decline, with no consensus among experts on how clinically meaningful it is and that this benefit has to be weighed against the harms of ARIA such that net benefit is uncertain.

Committee discussions and recommendations

The report was made available for public deliberation and the appraisal committee gathered to vote on the long-term value for money of lecanemab. A majority of the panel voted the evidence is not adequate to demonstrate that net health benefit of lecanemab added to supportive care is superior to supportive care alone. The panel had concerns around the amyloid hypothesis, clinical meaningfulness of the results and serious adverse events. ICER reports the treatment with lecanemab in MCI due to AD or mild AD as 'Promising but Inconclusive.'

Based on their review of the clinical evidence and consideration of the other benefits of treatment, the majority of the panel also found that lecanemab at its current pricing represents "low" long-term value for money.

After the voting session, a roundtable of experts including clinical experts, patient representatives, US payers and the manufacturer discussed pricing implications and recommendations for fair access to lecanemab.

The key recommendations from the discussion relevant to other settings include:

- All stakeholders have a responsibility to ensure new treatment options are introduced in a way that addresses the impact on health inequalities. Manufacturers should work with communities and patient groups to develop reliable methods for recruiting diverse populations with MCI and AD in clinical trials.

- Manufacturers should set initial prices according to value assessments from independent analysts to preserve access and affordability of new therapies.

- Patient groups, the manufacturer, clinicians, and clinical specialty societies should accurately describe the clinical benefits of lecanemab as a slowing of decline of cognition and function and avoid over-selling the potential benefit of treatment by using terms such as “improvement” or “return of quality of life” or “game changer” in all personal statements and advertising. Furthermore, there should not be an over-emphasis on the removal of amyloid from the brain, which still has not been conclusively linked to clinical outcomes.

- Payers should ensure coverage of PET scans and APOE4 genotype testing for accurate diagnosis of AD and risk stratification.

- Health systems should invest resources to increase capacity for screening and diagnosis and invest in infrastructure that will increase access to dementia care and infusion centres particularly in rural or underserved areas.

- Manufacturers should release all patient-level data to help patients, clinicians, researchers, and regulators to understand more about the link between amyloid reduction and cognitive outcomes.

Table 1. Description of models used in ICER's assessments of aducanumab and lecanemab.

	Aducanumab	**Lecanemab**
Model type and health states	Markov cohort model with MCI due to AD; mild AD; moderate AD; severe AD; and death.	Same as aducanumab
Population	Mean age of cohort is 70 years old based on the weighted average of patients in the ENGAGE and EMERGE trials	Mean age of cohort is 71 years old based on the mean age of patients in the CLARITY-AD trial
	Patients enter the model in “MCI due to AD” health state (55%) or “mild AD” health state (45%) with confirmed amyloid positivity. The proportions of patients starting the model in each clinical stage was based on Potashman et al (2020).	Same as aducanumab
Intervention	Aducanumab in addition to supportive care	Lecanemab in addition to supportive care
Comparator	Supportive care which was assumed to include non-pharmacological and pharmacological (but not disease-modifying) interventions	Same as aducanumab
Outcomes	Quality-adjusted life years (QALYs), equal-value life years (evLYs), life years (LYs), years living outside of long-term care, and costs.	Same as aducanumab
Perspective	Healthcare system and modified societal perspective	Same as aducanumab
Cycle length	1 year	Same as aducanumab
Time horizon	Lifetime	Same as aducanumab
Care setting	92% of the cohort assumed to start in a community care setting and the remaining 8% in long-term care. These proportions were based on published data. (Johnson, 2019)	Same as aducanumab

	Aducanumab	Lecanemab
Source of effectiveness and safety data	Weighted average (based on the sample sizes) of the results from the two pivotal phase 3 trials (ENGAGE and EMERGE)	phase 3 RCT CLARITY-AD

Table 2. Key modelling assumptions and results in ICER's cost-effectiveness assessments of aducanumab and lecanemab

	Aducanumab	Lecanemab	Additional notes/rationale
Key assumptions			
Effectiveness in reducing progression	Assumed to slow progression in patients in “MCI due to AD” and “mild AD” health states but not effective once patients progress to “moderate AD”. The relative effectiveness of aducanumab on changes in CDR-SB was used as proxy for its clinical effectiveness.	Same approach as aducanumab	In the aducanumab assessment report input from stakeholders was cited for the assumption that there is no expectation of impact of treatment in moderate AD while in the lecanemab assessment report the rationale provided was that both clinical expert input and trials of anti-amyloid treatments indicate this. Change in CDR-SB was the primary clinical endpoint in the pivotal trials for both treatments.

	Aducanumab	Lecanemab	Additional notes/rationale
	Aducanumab assumed to be 50% less effective in reducing progression from the “mild AD” health state compared to from the “MCI” health state	Lecanemab assumed to have the same effectiveness in slowing down disease progression from both the “MCI” and the “mild AD” health states	For aducanumab there was very limited evidence on its effectiveness on transition from “mild AD” to “moderate AD” based on the clinical characteristics and early disease stage of the trial participants and therefore an assumption was made and tested in sensitivity analyses. However, for lecanemab there was existing evidence from CLARITY-AD for both “MCI” and “mild AD”.
	No additional benefit assumed once patients discontinued treatment	Same assumption as aducanumab	There is a lack of robust evidence of benefit after treatment discontinuation.
Adverse events	ARIA-E and ARIA-H were included in the model. If patients experienced ARIA-E and ARIA-H simultaneously, they were assumed to experience one event. An ARIA event was assumed to last 12 weeks and therefore patients would require 3 additional MRIs when experiencing ARIA.	ARIA was included in the model as a whole group so a similar approach seems to have been taken as for aducanumab	These were the key adverse events associated with both the treatments and anti-amyloid treatments in general. The duration assumed was based on an FDA advisory board committee briefing document.(Food and Drug Administration, 2020)
Costs	Drug acquisition and administration costs, monitoring costs and the costs of managing	Same as aducanumab	

	Aducanumab	Lecanemab	Additional notes/rationale
	adverse events. Long-term care costs and other patient medical and pharmacy costs. The societal perspective scenario also included patient and caregiver productivity, and the health care costs of caregivers.		
Treatment discontinuation	Patients are assumed to stop receiving aducanumab once they enter the “severe AD” health state.	Patients are assumed to stop treatment in the model once they enter the “moderate AD” health state.	Clinical expert feedback informed assumptions for treatment stopping in both appraisals. There was a lack of robust evidence of additional clinical benefit after stopping treatment and therefore none was assumed.
	Treatment discontinued when patients experienced adverse events (ARIA) which was assumed to happen in the first 18 months	Treatment was discontinued when patients experienced adverse events (ARIA) which is assumed to occur in the first 6 months of receiving treatment	
	No additional benefit was assumed once patients stopped treatment	Same assumption as aducanumab	
Utility inputs	Health state utility values in the model were based on values reported Neumann et al.(Neumann *et al.*, 1999) For the societal perspective, the impact on carers was incorporated and utility values from Neumann at al. were adjusted according to disease severity based on	Same approach and inputs used	Values reported in Neumann 1999 were well-aligned with the model structure and approach given that they were stratified for patients and carers and based on care setting. Headache was the most reported symptom in symptomatic ARIA and

	Aducanumab	Lecanemab	Additional notes/rationale
	differences reported in Mesterton et al. (Mesterton *et al.*, 2010) Caregiver disutility was applied to patients' utility values with no caregiver disutility assumed upon patients' death. Patients were assumed to have a single, primary caregiver. Disutility associated with experiencing ARIA was assumed to be the same as experiencing a headache		therefore that was taken into account for estimating disutility.
Mortality	Age and sex-adjusted mortality rates were applied to patients in each model cycle, with an additional risk of death assumed according to severity of AD. The relative risks of death based on severity of AD were based on estimates identified in the literature	Same approach as aducanumab	
Results			
Base-case	**Healthcare perspective**: $1.14 million per QALY **Societal perspective:** $1.09 million per QALY	**Healthcare perspective**: $254,000 per QALY **Societal perspective**: $236,000 per QALY	There are more results reported in the respective reports related to additional scenario analyses that were carried out

	Aducanumab	Lecanemab	Additional notes/rationale
Probabilistic sensitivity analysis	Probability of aducanumab being cost-effective at a willingness-to-pay threshold of $150,000 and $200,000 per QALY was 0%	Probability of lecanemab being cost-effective was 1% and 21% at a willingness-to-pay of $150,000 and $200,000 per QALY, respectively from a healthcare perspective	
One-way sensitivity analysis	One-way sensitivity analysis from the healthcare perspective showed that the main driver of cost-effectiveness results was the effectiveness of the treatment in slowing progression of disease	The results of the one-way sensitivity analysis similarly show that treatment effectiveness is the main driver of the model from the healthcare perspective	

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