Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2700

lecanemab concentrate for solution for infusion (Leqembi®)

Eisai

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

lecanemab (Leqembi®) is not recommended for use within NHSScotland.

Indication under review: for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein E ε 4 (ApoEε4) heterozygotes or non-carriers.

In a randomised, double-blind, phase III study, lecanemab reduced the cognitive and functional decline associated with early Alzheimer's disease compared with placebo at 18 months.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.

The submitting company has indicated their intention to make a resubmission.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Lecanemab is a recombinant humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody which has high selectivity to amyloid beta aggregate species with preferential activity for toxic soluble amyloid beta protofibrils. Lecanemab binds to these aggregate amyloid beta species to neutralise and clear them from the brain. This reduces the amount of brain amyloid and amyloid-associated neurotoxicity, preserves neurones and delays worsening of the Alzheimer patient's condition.[1, 2]

Lecanemab is administered by intravenous infusion at a dose of 10 mg/kg once every 2 weeks and treatment should be discontinued when the patient progresses to moderate Alzheimer's disease.

In order to promote the safe and effective use of lecanemab, initiation of treatment in all patients should be through a central registration system implemented as part of a controlled access programme.[1]

1.2. Disease background

Alzheimer's disease is a progressive, neurological condition which is thought to be caused by an accumulation of proteins around brain cells. This includes beta amyloid which forms plaques and neurofibrillary tangles around brain cells disrupting neuron function. More than 90,000 people in Scotland are estimated to have dementia and Alzheimer's disease is the most common form of dementia, accounting for approximately 62% of cases.[3]

Alzheimer's disease progresses through several stages: preclinical, mild cognitive impairment, mild dementia, moderate dementia and severe dementia due to Alzheimer's disease. The diagnosis of mild cognitive impairment can be inconsistent due to lack of guidance, and furthermore can be challenging to attribute to Alzheimer's disease as early-stage symptoms can occur in many other clinical conditions. Recent Scottish Intercollegiate Guidelines Network (SIGN) guidelines define mild cognitive impairment due to Alzheimer's disease as "concern reflecting a change in cognition by the individual or an informant, with objective evidence of impairment in one or more cognitive domain, but with the preservation of independent functional abilities". Patients meeting this definition, in addition to having amyloid beta biomarkers on cerebrospinal fluid (CSF) immunoassay and neuronal injury on positron emission tomography (PET) scan, are the most likely to have mild cognitive impairment due to Alzheimer's disease.[3]

Dementia is typically characterised by memory impairment and in Alzheimer's disease is often accompanied by mental and behavioural symptoms. The SIGN guideline defines people with mild dementia as possibly able to live independently, but some supervision or support is often required. Judgement and problem solving are typically impaired but they may appear unimpaired to those who do not know them well.[3]

1.3. Treatment pathway and relevant comparators

There is currently no cure for Alzheimer's disease, but some medicines can relieve the symptoms including the acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine, which are licensed for the symptomatic treatment of mild to moderately severe Alzheimer's disease) and the N-methyl-D-aspartate antagonist (memantine, which is licensed for moderate to severe

Alzheimer's disease). The National Institute for Health and Care Excellence (NICE) guideline recommends donepezil, galantamine or rivastigmine for mild to moderate Alzheimer's disease and these recommendations are endorsed by SIGN. There are no specific guidelines or recommendations for patients with mild cognitive impairment due to Alzheimer's disease. Psychological treatments, including cognitive stimulation therapy, may help to support the memory, problem solving skills and language.[3, 4]

Lecanemab is the first disease-modifying medicine to be licensed for the treatment of early Alzheimer's disease. The submitting company considers standard of care (SoC), including symptomatic treatments, as the relevant comparator.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Lecanemab received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway on 17 February 2023 from the Medicines and Healthcare Products Regulatory Agency (MHRA).

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of lecanemab for the treatment of early Alzheimer's disease comes from the Clarity AD study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[2, 5]

Criteria	Clarity AD
Study design	A randomised, double-blind, multicentre, phase III study
Eligible patients	• patients aged 50 to 90 years • diagnosis of either MCI or mild dementia due to Alzheimer's disease: - diagnosis of MCI due to AD-intermediate likelihood, defined as meeting NIA-AA core clinical criteria for MCI due to AD - intermediate likelihood and global CDR score of 0.5 and a CDR Memory Box score of ≥0.5 at screening and baseline and history of subjective memory decline with gradual onset and slow progression over the previous year, corroborated by an informant or - diagnosis of mild AD dementia, defined as meeting NIA-AA core clinical criteria for probable AD dementia and global CDR score of 0.5 to 1 and a CDR Memory Box score of ≥0.5 at screening and baseline. • Objective impairment in episodic memory as indicated by at least one standard deviation below age adjusted mean in the WMS-IV LMII subscale • Positive biomarker for brain amyloid pathology: at least one of PET assessment or CSF assessment of t-tau or amyloid beta. • MMSE score ≥22 and ≤30 at screening and baseline. • BMI >17 and <35 at screening. • Have an identified study partner (caregiver) who will be able to support the patient and who spends ≥8 hours/week with the patient throughout the study.
Treatments	Lecanemab 10 mg/kg bodyweight or placebo IV infusion every 2 weeks for 18 months. Patients were allowed to continue to receive symptomatic treatment for AD (including acetylcholinesterase inhibitors and memantine or both) if they were on a stable dose for ≥12 weeks before baseline.

Randomisation	Patients were randomised equally to lecanemab or placebo with stratification for clinical subgroup (MCI due to AD or mild dementia due to AD), use of concomitant symptomatic medication for AD (yes or no), ApoEε4 status (carriers or non-carriers) and geographic location (North America, Europe or Asia-Pacific).
Primary outcome	Change from baseline to 18 months in the CDR-SB (interviews with patients and their care partners assessing six domains on cognition and function in AD; each domain is scored 0 to 3; total score ranges from 0 to 18 with higher scores indicating greater impairment; scores of 0.5 to 6 indicate early AD).
Key secondary outcomes	Change from baseline to 18 months in: •Amyloid burden on PET (sub-study; measures amyloid levels from tracers in centiloids). •ADAS-cog14 (cognitive scale assessing memory, language, orientation, ideational praxis and constructional praxis; range 0 to 90, with higher scores indicating greater impairment). •ADCOMS (includes 12 items from global CDR, MMSE and ADAS-cog14; range 0 to 1.97, with higher scores indicating greater impairment). •ADCS-MCI-ADL (18 items related to everyday activities which the carer reports as changes in function over a month's time period; range 0 to 53 with lower scores indicating greater impairment).
Statistical analysis	Efficacy analyses were performed in the mITT population which included all randomised patients who received at least one dose of study medicine and had a baseline and at least one post dose assessment of CDR-SB. A hierarchical statistical testing strategy was applied to the primary and key secondary outcomes in the Clarity AD study (mITT population) with no formal testing of outcomes after the first non-significant outcome in the hierarchy as ordered above.

Abbreviations: AD = Alzheimer's Disease; ADAS-cog14 = 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCOMS = Alzheimer's Disease composite Score; ADCS-MCI-ADL = Alzheimer's disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoEε4 = apolipoprotein E ε 4; BMI = body mass index; CDR = Clinical Dementia Rating; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CSF = cerebrospinal fluid; IV = intravenous; MCI = mild cognitive impairment; mITT = modified intention-to-treat; MMSE = Mini Mental State Examination; NIA-AA = National Institute on Aging-Alzheimer's Association; PET = Positron Emission Tomography; WMS-IV LMII = Wechsler Memory Scale IV Logical Memory II

In the modified intention-to-treat (mITT) population of Clarity AD, there was a statistically significantly smaller increase in mean Clinical Dementia Rating-Sum of Boxes (CDR-SB) score from baseline to 18 months in the lecanemab group compared with the placebo group. The submitting company noted that this represents a 27% lower decline in CDR-SB with lecanemab compared with placebo. The treatment difference was consistent across all six domains of the CDR-SB in the mITT population. However, lecanemab was not licensed for the full study population but instead for a subgroup of the mITT population, in patients who were ApoEε4 heterozygous or non-carriers and excluding those with ApoEε4 homozygous status. Results for the mITT population and this relevant subgroup (described as the licensed population) are presented in Table 2.2.[1, 2, 5]

Table 2.2: Results for the primary and key secondary outcomes in the Clarity AD study at 18 months.[1, 2, 5, 6]

	mITT population		Licensed population	
	Lecanemab (n=859)	**Placebo (n=875)**	**Lecanemab (n=723)**	**Placebo (n=743)**
Primary outcome: change from baseline mean CDR-SB				
Mean CDR-SB at baseline	3.17	3.22	3.17	3.22
Adjusted mean change in CDR-SB at 18 months	1.21	1.66	1.15	1.73
Difference versus placebo (95% CI)	-0.45 (-0.67 to -0.23), p<0.001		-0.58 (-0.81 to -0.35)	
Key secondary outcome: change from baseline in amyloid burden on PET				
	n=354	n=344	n=298	n=302
Mean amyloid burden at baseline, centiloids	77.9	75.0	*	*
Adjusted mean change	-55.5	3.64	*	*
Difference versus placebo (95% CI)	-59.1 (-62.6 to -55.6), p<0.001		*	
Key secondary outcome: change from baseline in ADAS-cog14				
	n=854	n=872	n=719	n=740
Mean ADAS-cog14 at baseline	24.45	24.37	24.48	24.40
Adjusted mean change	4.14	5.58	4.21	5.84
Difference versus placebo (95% CI)	-1.44 (-2.27 to -0.61), p<0.001		-1.63 (-2.56 to -0.71)	
Key secondary outcome: change from baseline in ADCOMS				
	n=857	n=875	*	*
Mean ADCOMS at baseline	0.398	0.400	*	*
Adjusted mean change	0.164	0.214	*	*
Difference versus placebo (95% CI)	-0.050 (-0.074 to -0.027), p<0.001		*	
Key secondary outcome: change from baseline in ADCS-MCI-ADL				
	n=783	n=796	n=656	n=675
Mean ADCS-MCI-ADL at baseline	41.2	40.9	41.3	40.9
Adjusted mean change	-3.48	-5.50	-3.47	-5.70
Difference versus placebo (95% CI)	2.02 (1.21 to 2.82), p<0.001		2.23 (1.34 to 3.13)	

Abbreviations: ADAS-cog14 = Alzheimer's Disease Assessment Scale–Cognitive subscale 14-item version; ADCOMS = Alzheimer's Disease Composite Score; ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ADCOMS = Alzheimer's Disease Composite Score; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CI = confidence interval; mITT = modified intention-to-treat; PET = Positron Emission Tomography.

**results for key secondary outcomes of amyloid burden and ADCOMS in the licensed population were considered confidential by the company.*

*Other data were also assessed but remain confidential.**

Time to worsening of global Clinical Dementia Rating (CDR) score at 18 months follow-up (defined as time from randomisation to time of worsening as an increase in global CDR score by ≥0.5 points for mild cognitive impairment patients and by ≥1.0 points for mild dementia patients) was assessed as an exploratory outcome in Clarity AD. In the mITT population, the risk of progression

to the next stage of Alzheimer's disease on global CDR was lower with lecanemab compared with placebo at 18 months; hazard ratio 0.69 (95% CI: 0.57 to 0.83). [2, 6]

**results for the licensed population were considered confidential by the company.*

*Other data were also assessed but remain confidential.**

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using exploratory outcomes of EQ-5D-5L Health Today score and the Quality of Life in Alzheimer's disease (QOL-AD) questionnaires at baseline and every 6 months by patients and carers. In addition, burden on caregiver was measured every six months using the Zarit's Burden Interview (ZBI).[5]

In the mITT population, the adjusted mean treatment difference in change from baseline to 18 months was improved for each of these outcomes: 2.02 in EQ-5D-5L assessed by patient (a 49% less decline) (in the patient-by-proxy assessment, the difference was smaller); 0.66 in QOL-AD total score by patient (a 56% less decline) and -2.21 in ZBI (a 38% less decline). There were similar improvements in the licensed population.[2, 5, 6]

2.3. Supportive studies

Patients who completed the 18-month, double-blind period of Clarity AD were able to enter an ongoing open-label extension study (Clarity AD OLE). All patients received open-label lecanemab 10 mg/kg every 2 weeks for up to 48 months, until the medicine is commercially available or until the benefit-to-risk assessment is no longer considered favourable, whichever occurs first. The primary efficacy outcome in the OLE was change in CDR-SB from baseline in the core study.

Interim data from 18-months follow-up of the OLE (36 months including Clarity AD core study) for 569 patients originally randomised to lecanemab (early start) and 549 patients originally randomised to placebo and switched to lecanemab at 18 months (late start) suggest that the change from baseline in CDR-SB continues. Data from an observational cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database similar in baseline demographics and clinical characteristics to the Clarity AD population suggest a difference in adjusted mean change from baseline to 36 months in CDR-SB of -0.95 between patients randomised to lecanemab in the core study (n=569) and this ADNI cohort (n=173).[2, 7]

**results for the licensed population were considered confidential by the company.*

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

At the end of the placebo-controlled, core period of the Clarity AD study, the median duration of treatment in both groups of the safety population (n=1,795) was 18.03 months. Any treatment-emergent adverse event (AE) was reported by 89% (798/898) of patients in the lecanemab group and 82% (735/897) in the placebo group and these were considered treatment-related in 45% and 22% respectively. In the lecanemab and placebo groups respectively, patients reporting a serious AE were 14% versus 11% and patients discontinuing therapy due to an AE was 6.9% versus 2.9%.

These incidences were similar in the safety population reflecting the licensed population (excluding patients with ApoEε4 homozygous status, n=1,521).[2, 5, 6]

In the licensed population, the incidence of the treatment-emergent AEs was generally similar between the lecanemab and placebo groups, with the exception of infusion-related reactions (26% versus 7.1%), amyloid-related imaging abnormalities-oedema (ARIA-E) and -haemosiderin deposition (ARIA-H), as detailed below. The incidence of ARIA was lower in the licensed population (ApoEε4 heterozygous and non-carrier patients) than in the ApoEε4 homozygous patients.[1]

ARIAs are an AE of special interest. In the licensed population, symptomatic ARIA was reported in 2.1% (16/757) of lecanemab treated patients with serious symptoms requiring hospitalisation occurring in three patients (0.4%). During the 18-month study period, clinical symptoms resolved in 12 patients. When asymptomatic radiographic events were included, ARIA was reported in 17% of patients on lecanemab compared to 7.2% (55/764) of patients on placebo.[1, 2]

ARIA-E (most commonly seen as temporary swelling in one or more areas of the brain) was observed in 8.9% of patients on lecanemab compared with 1.3% of patients on placebo. The majority of ARIA-E was asymptomatic, with symptomatic ARIA-E reported in 1.6% patients on lecanemab and no patients on placebo.[1]

ARIA-H (most commonly seen as small spots of bleeding in or on the surface of the brain) was observed in 13% of patients on lecanemab compared with 6.8% of patients on placebo. The majority of ARIA-H was asymptomatic, with symptomatic ARIA-H reported in 0.8% and 0.1% of patients respectively. ARIA-H and ARIA-E can occur together but there was no increase in isolated ARIA-H for lecanemab compared to placebo.[1]

The summary of product characteristics (SPC) provides recommendations for monitoring for ARIA.

In the licensed population, intracerebral haemorrhage was reported in 0.5% of lecanemab and 0.1% of placebo patients.[1]

The SPC recommends that lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Lecanemab is the first disease-modifying medicine to be licensed for the treatment of early Alzheimer's disease.[1]
- In the Clarity AD study, lecanemab reduced the rate of decline in the mean CDR-SB score from baseline to 18 months compared with placebo with a significant difference of -0.45 in the mITT population and a numerical difference of -0.58 in the licensed population. The treatment effect was consistent across all six domains of the CDR-SB in the mITT population, including memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care, and was greater than the estimated treatment difference of 0.373 in the study's statistical plan.[2, 5]
- Results for the primary outcome were supported by statistically significant improvements in the key secondary outcomes in the mITT population and numerical improvements in the

licensed population, including the amount of amyloid in the brain and measures of cognitive and functional ability.[2, 5]

- There were numerical improvements in the exploratory quality of life assessments favouring lecanemab over placebo to 18 months.[2]
- Uncontrolled data from the OLE of Clarity AD suggest that the treatment effect is maintained to 36 months.[2, 7]

4.2. Key uncertainties

- A treatment effect was not seen for lecanemab versus placebo in the primary outcome in patients with ApoEε4 homozygous status (15% of mITT population) and these patients were excluded from the licensed population. Results of additional analyses of Clarity AD, excluding patients with ApoEε4 homozygous status, support the licensed indication. These subgroup analyses were performed post hoc, and although results favoured lecanemab over placebo, are considered descriptive only.[1, 2]
- The treatment effect of lecanemab on CDR-SB was modest. The CDR-SB score also declined in patients in the lecanemab group but not as much as in patients in the placebo group. There is no agreed definition of a clinically meaningful treatment difference in this outcome and there are differences in opinion over whether the Clarity AD results are clinically meaningful. The CDR-SB scale increases by increments of ≥0.5 points with clinical progression (≥0.5 points in the early stages and ≥1 points in the more advanced stages). Although a 0.5 point increase in CDR-SB scores indicates some decline in function in an overall population, the clinical relevance in the individual patient will depend on the stage of disease, the magnitude of decline and on which of the six domains are mainly affected. While a treatment effect was seen across all six CDR-SB domains in Clarity AD, this may differ in individual patients in practice who have one domain affected more than another. The MHRA did consider the results to be clinically meaningful but the overall benefit was described as modest. The results were considered to support a degree of disease modification in early Alzheimer's disease but were not considered currently robust enough to support a disease-modifying indication. The exploratory outcome of time to worsening in global CDR and a progressor analysis submitted to the MHRA, which compared the proportion of patients who progressed on CDR-SB by thresholds of 0.5 points in the lecanemab and placebo groups, indicated less progression with lecanemab.[2, 5, 8]
- The primary outcome of change in CDR-SB is a validated outcome in studies in Alzheimer's disease.[5] However, clinical experts consulted by SMC advised that this is not used to assess patients in practice.
- The controlled period of the Clarity AD study was limited to 18 months which is short to determine the relative treatment effect of a progressive condition. Although further data from the Clarity AD OLE suggest that the treatment effect is maintained, these longer term data are uncontrolled. Analysis of the indirect comparison with a cohort of patients from the ADNI database presented by the submitting company is limited by few details on demographics and matching, making it considerably uncertain.[2, 5]

- There was an increased incidence of ARIAs in patients treated with lecanemab compared with placebo. Longer term safety data are awaited from the Clarity AD OLE and a post–authorisation study. A controlled access programme will be implemented for initiation of lecanemab in all patients.[1, 2]
- In Clarity AD, 62% of study patients had mild cognitive impairment and 38% had mild dementia due to Alzheimer's disease.[5] Clinical experts consulted by SMC considered that the respective definitions used in the study (detailed in Table 2.1) are not reflective of how these patients are diagnosed in NHSScotland, which may have implications for identifying eligible patients in practice.
- Study patients were allowed to continue to take stable doses of symptomatic treatments for Alzheimer's disease during Clarity AD. Fifty-three percent of patients were taking symptomatic treatment at baseline and the treatment effect looked similar to those who were not.[5] This may affect the generalisability of study results to clinical practice, since no symptomatic treatments are currently licensed for mild cognitive impairment and memantine is only licensed for the treatment of moderate or severe Alzheimer's disease, although there may be off-label use.

4.3. Innovative Licensing and Access Pathway (ILAP) and ongoing studies

Further data are awaited from the OLE of Clarity AD. In addition, the submitting company is to perform a post-authorisation safety study to assess the safety and benefit-risk profile of lecanemab in routine clinical practice particularly in relation to the incidence and severity of ARIAs and intracranial haemorrhage and long-term safety. An additional study (303) will assess the efficacy (brain volumes) and safety of lecanemab in preclinical Alzheimer's disease.[2] However, the New Drugs Committee considered that data from ongoing studies are unlikely to address uncertainty in the clinical relevance in the modest treatment benefit seen in Clarity AD.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that there is an unmet need for disease-modifying medicines for early Alzheimer's disease in Scotland. They considered that lecanemab is a therapeutic advancement in offering a treatment that may slow the progression of Alzheimer's disease but noted that the treatment effect is small, side effects are concerning and that longer term data are needed.

4.5. Service implications

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information**.**

Diagnostic testing, using PET scans or CSF analysis to confirm amyloid beta pathology, is required to identify eligible patients. In addition, genetic testing of ApoEε4 phenotype to confirm heterozygous or non-carrier status is also required to meet the marketing authorisation. Brain MRI scans are needed before starting lecanemab and during treatment, as detailed in the SPC, in order to monitor for potential ARIA-E and ARIA-H. These diagnostic tests and MRI access are expected to have a substantial impact on services. The administration of lecanemab requires intravenous infusion every 2 weeks and this has implications for patients, carers and the service.[1] Clinical

experts consulted by SMC highlighted that these requirements would make it challenging to introduce lecanemab into practice.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from Alzheimer's Research UK, Alzheimer Scotland and Dementia UK. All three organisations are registered charities.
- Alzheimer's Research UK has received 0.6% pharmaceutical company funding in the past two years, including from the submitting company. Alzheimer Scotland has received 0.34% pharmaceutical company funding in the past two years, with none from the submitting company. Dementia UK has not received any pharmaceutical company funding in the past two years.
- Living with Alzheimer's disease is a complex, unique experience that affects every aspect of a person's ability to function day-to-day. In addition to the physical and cognitive changes experienced as the condition progresses, people with Alzheimer's disease also experience significant emotional and social challenges which affects their quality of life, often facing stigma and misunderstanding. It also has a profound impact on the physical and mental health of carers, with most of the financial burden falling on families.
- There are currently a few licensed medications available for the treatment of the symptoms of Alzheimer's disease. The effectiveness of the medications available is variable, they can have side effects and do not work for everybody. None of these treatments address the underlying causes of Alzheimer's disease.
- Lecanemab represents a new class of treatment for mild cognitive impairment due to Alzheimer's disease which could alter the natural course of the condition. It has the potential to be the catalyst for delivering a step change in the diagnosis and care of those with Alzheimer's.
- Lecanemab may bring improvements to the quality of life for those with mild to moderate Alzheimer's disease, such as slowing the progression of the condition and providing more time to plan for the future.
- Lecanemab gives patients and their families hope for the future. However, there are concerns about the negative side effects and safety concerns of this treatment which would require close monitoring.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

Details of the economic case are summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	30 years.
Population	Patients with MCI and mild dementia due AD and who are ApoEε4 heterozygotes or non-carriers and confirmed Aβ pathology.
Comparators	Lecanemab was considered as an add-on therapy to SoC. SoC was also the only included comparator. SoC consisted of pharmacological interventions and non-pharmacological interventions. Pharmacological interventions included in the model were donepezil, rivastigmine, galantamine and memantine. Non-pharmacological interventions were not explicitly included, but their effects on the economics were assumed to be captured implicitly through the efficacy, cost and outcomes data used.
Model description	The analysis used a Markov model, which traced the progression of AD across a patient's life span. The included health states were MCI due to AD, mild AD, moderate AD, severe AD and death. CDR-SB score was used to define health states in the base case. The model considered all the alive health states across 2 separate settings, the community setting and the institutional setting, leading to a total of 9 health states. The model structure allowed for the possibility of backward transitions (i.e. from more severe health states to less severe health states), however patients could not return to the community setting once institutionalised. All patients started in the MCI due to AD or mild AD states. The distribution of patients across those states was based on clinical opinion. The submitting company considered these proportions as representative of the current treatment population, with more mild AD patients treated than MCI due to AD patients. However, the submitting company also noted an expectation that these proportions would shift over time as diagnosis of MCI due to AD improves in light of an additional possible treatment option.
Clinical data	The main source of clinical evidence was the Clarity AD study.[5] Transition probabilities over the first 18 months of the model were estimated directly from the study data using a multistate survival model.
Extrapolation	All transitions in the post-18-month period were derived from a US longitudinal study of AD patients.[9] The 12-month transition probabilities estimated within that study were converted to monthly transition probabilities. Those monthly transition probabilities were applied directly to model movements in the SoC arm. The same transition probabilities were applied for lecanemab patients, but only after adjustment for a treatment effect. That treatment effect was estimated based on time to worsening CDR-SB scores in the Clarity AD study, with separate hazard ratios for the MCI due to AD and mild AD populations. Patients were subject to a risk of institutionalisation, estimated from Knapp et al. (2016).[10] This risk increased in line with AD severity. Lecanemab patients would receive treatment until discontinuing or meeting a stopping rule. Discontinuation was modelled as a constant rate based on that observed in the Clarity AD study. Patients were assumed to stop treatment with lecanemab upon entrance to the moderate or severe states or upon the occurrence of a second stopping rule the submitting company classified as commercial-in-confidence, and so cannot be reported. Mortality was estimated by applying separate standardised mortality ratios for each health state to the mortality rate of the Scottish population.[11] The source employed estimated that the mortality rate within the MCI due to AD population was below that of the general population. This lacked face validity and so the mortality rate in the MCI due to AD state was set equal to that of the general population.
Quality of life	The base case analysis used data collected from carers as a proxy for patients themselves, using the EQ-5D-5L questionnaire. Data was mapped to EQ-5D-3L values for use in the economics. Data from the Clarity AD study was used to inform utility values in the MCI and mild AD states. Utility values in the moderate and severe AD states were based on an external source.[12] There were additionally applied disutilities for institutionalisation and AEs.

	The submitting company argued that given the burden that AD can place on carers, that health impacts for carers should be included within the base case analysis. This was inconsistent with SMC guidance, but carer impacts were explored in scenario analysis.
Costs and resource use	Medicine costs in the model included testing, acquisition, administration and AE costs. Wider costs included in the model were for monitoring as well as costs to the NHS and social care sector for the care of patients with AD.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The economic analysis suggested that lecanemab was associated with increased costs but also improved health outcomes relative to SoC. The main cost difference between lecanemab and SoC was the higher acquisition costs of lecanemab. Lecanemab was estimated at generating better health outcomes for the patient by maintaining them in the less severe health states for longer. SMC is unable to present the incremental cost-effectiveness ratio (ICER) for the comparison between lecanemab and SoC as the submitting company considers this information commercial-in-confidence.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

The company conducted one-way sensitivity analysis, probabilistic sensitivity analysis and scenario analysis to explore uncertainty. That analysis suggested that the long-term treatment effect of lecanemab, the discontinuation rate and the utility values in the model were key drivers of the economic outcomes. Descriptions of the key scenarios considered as part of the decision-making are provided in Table 6.3 below. SMC is unable to present the ICER values as the submitting company considers this information commercial-in-confidence.

Table 6.3 Scenario analysis

	Parameter	**Base case**	**Scenario**	**ICER (£/QALY)**
-	Base case			CiC
1	Time horizon	30 years	20 years	CiC
2			10 years	CiC
3	Patient population	MCI and Mild AD	MCI only	CiC
4			Mild AD only	CiC
5	Backward transitions	Allowed	Not allowed	CiC
6	Stopping rules	Two stopping rules: 1) Upon entrance to moderate or severe states 2) Confidential stopping rule	No stopping rule 1	CiC
7			No stopping rule 2	CiC
8			No stopping rule 1 or 2	CiC
9	Source of transition probabilities from 18 to 36 months	Natural history model	Multistate model based on Clarity AD OLE	CiC
10	Patient utility	Clarity AD/Farina et al (2020)[5, 12]	Landeiro et al. (2020)[13]	CiC
11	Caregiver health outcomes	Excluded	Utility decrement	CiC
12			Utility increments	CiC

	Combined scenarios	
13	• Time horizon of 20 years (scenario 1) • Backward transitions not allowed (Scenario 5) • Patient utility from Landerio et al (2020) (scenario 10)	CiC
14	• Time horizon of 20 years (scenario 1) • Backward transitions not allowed (Scenario 5) • No stopping rule at moderate/severe state (Scenario 6) • Patient utility from Landerio et al (2020) (scenario 10)	CiC
15	• Time horizon of 20 years (scenario 1) • Backward transitions not allowed (Scenario 5) • Patient utility from Landerio et al (2020) (scenario 10) • Carer disutility included through utility increments (Scenario 12)	CiC

Abbreviations: incr. – Incremental; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; MCI – mild cognitive impairment; AD – Alzheimer's disease; SMR – standardised mortality ratio; CiC – commercial-in-confidence

6.4. Key strengths

- The modelled population matches the licensed indication.
- The central clinical study provided directly observed efficacy data against the relevant comparator of standard care.
- The model structure, in regard to the included states, appeared to be reasonable.

6.5. Key uncertainties

- There is a high degree of extrapolation within the model. The observation period of Clarity AD was 18 months, much shorter than the 30-year time horizon of the model. This degree of projection, and the assumptions employed across the duration of the model regarding treatment effect, produced uncertainty over the economic results. Based on this uncertainty, the strength of the clinical data and the consideration that AD is a life limiting condition, shorter time horizons were considered informative for decision-making (see Scenarios 1 and 2 in Table 6.3).
- The analysis utilised two stopping rules, which limited the duration of treatment with lecanemab. One of those rules, which stated that lecanemab treatment would stop when a patient's AD became moderate or severe, was specified in the marketing authorisation. The second stopping rule, which the submitting company classified as confidential, was included based on expert clinical feedback received by the submitting company. Despite this, there were concerns that once treatment had been initiated, it would be challenging to stop because of limited alternative treatments. Scenarios removing the stopping rules led to large increases in the ICER (Scenarios 6 to 8), although these may be considered overly conservative as at least some patients are likely to cease treatment at the modelled stopping points.
- Within the base case modelling some patients undertook backward transitions, meaning they moved from more to less severe states. These movements were informed by the clinical data sources, where some patients did see improvements in their condition. Given that these improvements in condition are reasonably expected to be temporary, the

change in the ICER when backward transitions were not allowed (Scenario 5) was an area of concern.

- There was concern that bias may have been introduced from the estimation of transition probabilities for the period of the model after 18 months. Across that period monthly transitions were estimated based on 12-month transitions which were disaggregated into monthly transitions and then reapplied. This can result in dynamics inconsistent with the original sources. Overall, it is unclear that the model would accurately match the patient progression that was observed in the original data source. The submitting company explored an alternative approach which applied a multistate survival model to longer term data from the Clarity AD open-label extension. This generated transition probabilities for the period between 18 and 36 months. Applying this increased the ICER slightly (Scenario 9), but it did not address the possible bias that would remain in the transition probabilities applied after 36 months. The scale and direction of any introduced bias was unknown.
- The utility value for patients in the MCI due to AD state was above what would be expected in general population. This was seen as lacking face validity. The submitting company provided a scenario using an alternative single source, which lowered the utility for patients across all states and brough the starting utility values below those for the general population. This increased the ICER slightly (Scenario 10).
- The submitting company noted that AD is associated with significant carer burden and so they explored the health impacts to carers. In line with SMC guidance these impacts were not included in the base case analysis but provided as a scenario. There was some uncertainty over the best approach to capture the effects on carers. The standard approach, where higher carer disutility decrements were applied for worse health states reduced the ICER (Scenario 11). The submitting company argued that this failed to capture the true benefits of lecanemab, as these decrements were applied as long as the patient remained alive, in effect penalising the survival advantage generated by lecanemab treatment. An alternative approach was to apply higher carer utility increments to better health states, which lowered the ICER further (Scenario 12). In turn this may overestimate the benefits of lecanemab on carers, by implying that caring brings health benefits over not providing care when a patient dies. Each approach has limitations and the range between the two scenarios was seen as informative.

7. Conclusion

After considering all the available evidence, the Committee was unable to accept lecanemab for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline SIGN 168: Assessment, diagnosis, care and support for people with dementia and their carers in November 2023.[3]

The National Institute for Health and Care Excellence (NICE) published NICE guideline 97: Dementia: assessment, management and support for people living with dementia and their carers, in June 2018.[4]

9. Additional Information

9.1. Product availability date

28 October 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
lecanemab	**10 mg/kg intravenous infusion every 2 weeks**	**21,320**

Costs from eMC Dictionary of Medicines and Devices Browser on 22 October 2024. Costs calculated based on a 70 kg adult and using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 3,572 patients eligible for treatment with lecanemab in year 1 and 3,450 in year 5.

SMC is unable to publish the with PAS budget impact due to commercial-in-confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 13 December 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial-in-confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.