NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lecanemab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: August 2024

Note that this document is not NICE's final guidance on lecanemab. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using lecanemab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 20 September 2024
- Second evaluation committee meeting: To be confirmed.
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Lecanemab is not recommended, within its marketing authorisation, for treating mild cognitive impairment and mild dementia due to Alzheimer's disease in adults who are apolipoprotein (APO) E4 heterozygotes or non-carriers.

1.2 This recommendation is not intended to affect treatment with lecanemab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for mild cognitive impairment caused by Alzheimer's disease is best supportive care, and for mild dementia caused by Alzheimer's disease includes an acetylcholinesterase inhibitor (donepezil hydrochloride, galantamine or rivastigmine). Lecanemab could be used at the same time as current treatments at these stages of Alzheimer's disease.

Evidence from a clinical trial suggests that people having lecanemab continue to have worsening cognitive function over time, but at a slower rate than people on placebo (both added to current treatment). There is a lack of evidence on the long-term effects.

There are substantial uncertainties in the economic model, such as:

- how changes in a person's condition are modelled over time, including when they stop treatment
- the infusion costs for lecanemab.

Although there are uncertainties with the cost effectiveness estimates, all of the cost-effectiveness results seen by the committee are considerably above what NICE

considers an acceptable use of NHS resources. So, lecanemab cannot be recommended for routine use.

NICE has asked the company and NHS England to provide some additional information to address the uncertainties. The committee will consider this information and other stakeholder comments at a second meeting.

2 Information about lecanemab

Marketing authorisation indication

2.1 Lecanemab (Leqembi, Eisai) is indicated 'for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for lecanemab.

Price

2.3 The list price of lecanemab powder for concentrate for solution for infusion is confidential until published by the Department for Health and Social Care.

2.4 The company has a commercial arrangement, which would have applied if the lecanemab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Eisai, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence. The first committee meeting was held before the full detail of the marketing authorisation for lecanemab from the Medicines and Healthcare products Regulatory Agency was

available. The committee discussion was based on the full population in the Clarity AD trial, but subgroup analysis based on apolipoprotein (APO) E4 carrier status was also considered.

The condition

Alzheimer's disease

3.1 Alzheimer's disease is a progressive neurological condition, and the most common type of dementia. It affects 6 in 10 people with dementia, which is the leading cause of death in the UK. Alzheimer's disease is thought to be caused by the abnormal build-up of proteins in and around brain cells. One of these proteins is called amyloid beta. Deposits of amyloid proteins form plaques around brain cells and disrupt neurone function. The largest risk factor for dementia is age. More than 95% of people affected are over 65 years. The apolipoprotein (APO) E4 gene has also been associated with an increased risk of developing Alzheimer's disease. The patient experts explained that Alzheimer's disease affects people in different ways and advised against making general assumptions for all people with the condition. The patient expert statements described the loss of independence and confidence when they had their Alzheimer's disease diagnosis, and the hope that a first potential disease-modifying treatment would bring. The patient experts also identified the significant role of carers in looking after people with Alzheimer's disease, and the life-changing effects of the condition on them. Statements from carers of people with the condition described the stress and "desperation" associated with becoming a full-time carer. The clinical experts explained that Alzheimer's disease is progressive and complex, and is not fully understood. They added that the underlying pathology starts at least 10 years before symptoms present. The committee recalled the first-hand experiences shared by people with Alzheimer's disease. It concluded that the condition is progressive and debilitating, and affects people with it in different but significant ways. It also noted the substantial burden on the families and carers of people with the condition.

Diagnosing mild cognitive impairment and mild dementia caused by Alzheimer's disease

3.2 NICE's guideline on assessment, management and support for people living with dementia and their carers outlines recommendations for diagnosis of Alzheimer's disease in the NHS. But, the clinical and patient experts explained that NICE's guidelines are not always followed in clinical practice. This is because of challenges in accessing the recommended diagnostics and specialist services in some areas. Also, NICE's guideline does not include mild cognitive impairment (MCI) caused by Alzheimer's disease, which refers to the set of symptoms that occur before the dementia stage of the condition. Guidelines from the National Institute on Aging and the Alzheimer's Association define the MCI stage as mild changes in memory and thinking that are:

- noticeable and measurable
- do not disrupt a person's day-to-day life.

Mild dementia caused by Alzheimer's disease is defined as impairments in memory, thinking and behaviours that decrease a person's ability to function in day-to-day life. Alzheimer's disease usually develops slowly from initial symptoms. Progression is characterised by deterioration in cognition and functional ability, and associated behavioural and psychiatric symptoms. Alzheimer's disease can be confirmed by the presence of amyloid beta in the brain. This is tested for using a positron emission tomography (PET) scan or cerebrospinal fluid (CSF) test. The number of people diagnosed with mild dementia because of Alzheimer's disease in England is about 80,000. More than a third of people with all types of dementia in England do not have a dementia diagnosis. The exact number of people with MCI caused by Alzheimer's disease is unknown. But it is estimated to be present in about 5% of people over 65 years and about 25% of people over 80 years. The clinical experts emphasised that all people with MCI caused by Alzheimer's disease eventually progress to having dementia. They noted that most people do

not have a confirmed diagnosis of MCI, and that there are no standardised measures to clearly separate the disease stages. They explained that some people diagnosed with MCI caused by Alzheimer's disease in the NHS are followed up. But, many people are discharged from memory clinics back to primary care, with the advice to be rereferred once their symptoms progress. The patient experts noted the results of a survey done by a patient organisation showing that about 90% of people would want to have an accurate diagnosis, even if there were no treatments available. The committee noted that there are challenges with the diagnosis of MCI and mild dementia caused by Alzheimer's disease in NHS clinical practice. But, it recognised that diagnostic guidelines were not within its remit.

Clinical management

Treatment options

3.3 There are currently no pharmacological treatments for MCI caused by Alzheimer's disease. NICE's guideline on dementia and NICE's technology appraisal guidance on donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease recommend as options:

- the acetylcholinesterase inhibitors donepezil hydrochloride, galantamine and rivastigmine, all alone, for mild to moderate disease
- memantine alone:
  - for moderate Alzheimer's disease, when there is an intolerance or contraindication to acetylcholinesterase inhibitors
  - for severe Alzheimer's disease

For people with an established diagnosis of Alzheimer's disease already on an acetylcholinesterase inhibitor, they recommend as options:

- adding memantine for moderate disease
- adding memantine for severe disease.

The clinical experts explained that current treatments for Alzheimer's disease have symptomatic benefits for some people. But, none of the options available are disease-modifying. The committee concluded that current treatment options are very limited for mild dementia caused by Alzheimer's disease. It also concluded that there is a significant unmet need for treatment options to prevent progression to mild dementia caused by Alzheimer's disease.

Treatment positioning of lecanemab

3.4 The patient, clinical and commissioning experts highlighted that using lecanemab (and other disease-modifying treatments) in the NHS would require significant changes to the existing diagnostic pathway (see section 3.2). An outline of the new diagnostic pathway can be seen in the committee papers in the submission from NHS England. The changes recommended include:

- establishing specialist diagnostic clinics
- confirmatory diagnostic tests for amyloid beta pathology in cerebral spinal fluid (lumbar puncture) or with a PET-CT scan
- genetic testing for APOE4.

NHS England also noted that introducing disease-modifying treatments would substantially increase demand on primary care and memory clinics because of increased awareness of MCI and availability of treatment options. The committee heard that a blood test for amyloid beta is being developed, but noted that it was not currently available. People with MCI and mild dementia caused by Alzheimer's disease with confirmed amyloid pathology would be eligible to have lecanemab alongside established clinical management, including existing treatments. Commissioning experts identified that the treatment pathway for lecanemab would be more complex than for current treatments, and would include:

- 2-weekly intravenous infusions of lecanemab, started in secondary care
- routine outpatient follow-up appointments every 3 months

- routine MRIs during treatment
- acute management of amyloid-related imaging abnormalities, including additional MRIs (if needed).

The committee concluded that lecanemab (if recommended) would need a significant change to current diagnostic and treatment pathways in Alzheimer's disease.

Clinical effectiveness

Clarity AD trial

3.5 The main source of clinical-effectiveness evidence for lecanemab was the Clarity AD trial. This was a phase 3, randomised placebo-controlled double-blind trial. It investigated the efficacy of lecanemab compared with placebo in people aged 50 to 90 years with early Alzheimer's disease dementia. The trial recruited 1,795 people, 1,486 completed the 18-month study and, of these, 729 had lecanemab and 757 had placebo. The mean age was 71 years and 52% of people in the trial were women. The trial was carried out in 235 sites around the world, including 8 sites in the UK. The primary outcome was change in clinical dementia rating scale sum of boxes (CDR-SB) at 18 months from baseline. This 5-point scale characterises cognitive and functional performance across 6 domains (memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care). At 18 months, people in the lecanemab arm had an adjusted mean change in CDR-SB of 1.213 compared with 1.663 for placebo. This resulted in an adjusted mean difference between arms of -0.451 (-27.1%, p=0.00005) in the intention-to-treat full analysis set. The company explained that this meant lecanemab reduced the decline in CDR-SB by 27% at 18 months. The committee questioned the appropriateness of assuming that missing values in the trial were missing at random. The company explained that it explored this assumption in sensitivity analyses, including assuming that people who were missing to follow up progressed to moderate AD. It noted that

varying this assumption only had a very small impact on the cost-effectiveness results. The committee concluded that Clarity AD was relevant for the decision problem and investigating lecanemab for treating MCI or mild dementia caused by Alzheimer's disease.

Clinically meaningful treatment effect

3.6 The EAG and the submission from the Faculty of Public Health questioned whether the treatment effect of lecanemab was clinically meaningful. The Faculty of Public Health submission explained that literature suggests a minimum clinically important CDR-SB difference is 0.98 for MCI and 1.63 for mild dementia caused by Alzheimer's. The treatment effect seen with lecanemab in Clarity AD was smaller than both of these values. It also noted that the observed treatment effect for lecanemab at 18 months was about half of the treatment effect that is seen with current treatments at 6 months. But, the patient and clinical experts explained that it was inappropriate to directly compare the treatment effect of lecanemab with that of the acetylcholinesterase inhibitors and memantine. This was because lecanemab is disease-modifying and has a different mechanism of action from these treatments. The submissions from the Royal College of Psychiatrists and Association of British Neurologists considered that the observed treatment effect of lecanemab was clinically meaningful. They noted that it equated to a slowing in disease progression of between 4 and 6 months. Clinical experts consulted by the EAG also identified that a difference in CDR-SB of 0.451 would be seen as a clinically meaningful change by people with Alzheimer's disease. The company explained that lecanemab is a disease-modifying treatment, so the full long-term benefits of lecanemab may not be apparent at 18 months. It showed evidence that, at 24 months, people who had started Clarity AD on lecanemab had a 16% slower decline in CDR-SB than people who switched from placebo to lecanemab after the trial at 18 months. The committee noted that the observed treatment effect of 0.451 was the average effect across the full intention-to-treat population in the trial. The patient and clinical experts

noted that Alzheimer's disease is a highly heterogeneous disease. So, some people may experience a clinically meaningful slowing of disease progression when having lecanemab but others may not. They added that a larger treatment effect may also be seen at earlier disease stages. The clinical experts noted that CDR-SB is commonly used as an outcome measure for moderate to severe Alzheimer's disease. But, they explained that it is not very sensitive in detecting changes in early Alzheimer's disease, particularly for people with MCI. The committee noted that 1 increment on the CDR-SB scale is 0.5. The clinical experts added that a 0.5 change in CDR-SB can mean a change from benign forgetfulness to losing daily independence for some people. So, they said that a 0.5 change in CDR-SB can be clinically meaningful, particularly for younger people or people with fewer comorbidities. The patient and clinical experts agreed that a 6-month delay in disease progression was a clinically meaningful difference. They thought that a 4- or 5-month difference was also likely to be meaningful. The patient experts added that any slowing of disease worsening would be meaningful because it would mean more time socialising, driving and being independent. The committee concluded that lecanemab had a clinically significant treatment effect. But, it noted that the treatment effect was small and less than 1 increment on the CDR-SB scale (0.5). It understood that this may have been because of a lack of sensitivity for CDR-SB to detect disease changes for people with MCI. It also noted that it was unclear how heterogenous the results were. So, it concluded it would like to see:

- the distribution of change in CDR-SB score from baseline at 18 months, compared for lecanemab and placebo arms
- the mean difference from baseline by treatment arm at 18 months for the 6 individual domains of CDR-SB
- the least-squares mean change from baseline in EQ-5D-5L health-related quality-of-life values, by treatment arm, analysed using a mixed effects model with repeated measures.

Standard care in the trial

3.7 The EAG noted that treatments used alongside lecanemab in Clarity AD were different to those specified in the decision problem and EAG's clinical expert opinion of NHS clinical practice. The decision problem identified that non-pharmacological treatments are used for people with MCI caused by Alzheimer's disease and acetylcholinesterase inhibitors are used for people with mild dementia caused by Alzheimer's disease. The EAG's clinical expert largely agreed, estimating that:

- For people with MCI caused by Alzheimer's disease, a minority have acetylcholinesterase inhibitors and almost none have memantine.
- For people with mild dementia caused by Alzheimer's disease, 70% have acetylcholinesterase inhibitors and 5% have memantine.

The company shared the proportion of people in Clarity AD who had acetylcholinesterase inhibitors and memantine. The figures are confidential and cannot be reported here. But they argued that the figures largely aligned with real-world usage figures in Europe from Garcia et al. (2023). The study reported that:

- For people with MCI caused by Alzheimer's disease, 31% had acetylcholinesterase inhibitors and 8% had memantine.
- For people with mild dementia caused by Alzheimer's disease, 89% had acetylcholinesterase inhibitors and 7% to 21% had memantine.

At the EAG's request, the company shared CDR-SB results from Clarity AD for people with MCI excluding people who had an acetylcholinesterase inhibitors or memantine. It also shared results for people with mild dementia excluding people who had memantine. The results are confidential and cannot be reported here. The EAG noted that there was a reduction in the treatment effect of lecanemab when people who had acetylcholinesterase inhibitors or memantine were excluded from the analysis. But, the EAG noted that these results should be interpreted with caution because of the small sample size and lack of statistical

power. The clinical experts explained that lecanemab is given alongside current treatments and its mechanism of action is different from other treatments. So, they would not expect the use of other treatments to significantly change the treatment effect of lecanemab. The committee recalled that people with MCI caused by Alzheimer's disease have no current treatment options. But, people with mild dementia caused by Alzheimer's disease can have an acetylcholinesterase inhibitor (see section 3.3). It noted that there were differences in the treatments used as standard care in Clarity AD compared with what is used in NHS clinical practice. The committee concluded that it was acceptable to use the Clarity AD trial population for decision making. But it acknowledged that the differences in the treatments used in Clarity AD compared with NHS clinical practice increased the uncertainty.

Trial generalisability

3.8 The EAG questioned the generalisability of Clarity AD to NHS clinical practice. The clinical expert consulted by the EAG noted that the proportion of people with MCI and mild dementia caused by Alzheimer's disease in the UK is likely different to that reported in Clarity AD. The trial reported that 62% of people had MCI and 38% had mild dementia, which is what the company assumed in its economic model base case. But based on the clinical expert opinion, the EAG assumed that 38% of people had MCI and 62% had mild dementia in its base case. The EAG's clinical expert also noted that the primary outcome of CDR-SB is not used in UK clinical practice. Submissions from the Faculty of Public Health questioned whether functional unblinding might be a concern because of very different rates of infusion reactions for lecanemab (26.4%) and placebo (7.4%). The submissions also noted that baseline characteristics and the way people were diagnosed in the trial were different to the UK. The company explained that trial investigators were blinded to the occurrence of adverse events. It also added that the Clarity AD baseline characteristics were considered generalisable to the UK by the clinical experts it consulted. During the committee meeting, the clinical experts

highlighted that MCI caused by Alzheimer's disease is rarely diagnosed in the UK (see section 3.2), so the number of people with this condition is not known. They added that the number of people diagnosed with MCI will likely increase if lecanemab is recommended. The clinical experts explained that, although CDR-SB is not used in UK clinical practice, there is no consensus on what measure should be used. They also added that they would expect the observed treatment effect of lecanemab to be realised in UK clinical practice. The committee considered whether Clarity AD is generalisable to UK clinical practice. It recalled its conclusion on the generalisability of trial comparators (see section 3.7). It noted that the proportion of people with MCI and mild dementia caused by Alzheimer's disease in the UK was unknown and likely to change. It also noted that, although CDR-SB is not an outcome used in clinical practice, there are no alternative measures that are considered more suitable. So, the committee concluded that Clarity AD is generalisable to UK clinical practice. But, it would like to see estimates from clinical experts on what the introduction of lecanemab would do to the number of people who are diagnosed with MCI or mild dementia caused by Alzheimer's disease.

Treatment effects for subgroups

3.9 The company shared treatment-effect results for lecanemab from Clarity AD, split by subgroups for APOE4 carrier status and age. The adjusted mean differences in CDR-SB by APOE4 carrier status were:

- non-carriers: -0.75 (41% slowing of decline)
- heterozygote, 1 copy of the gene: -0.50 (30% slowing of decline)
- homozygote, 2 copies of the gene: 0.28 (22% faster decline, confidence interval crosses zero).

The adjusted mean differences in CDR-SB by age were:

- 75 years and over: -0.72 (40% slowing of decline)
- 65 to 74 years: -0.37 (23% slowing of decline)

- under 65 years: -0.08 (6% slowing of decline, confidence interval crosses zero).

The committee questioned whether the larger treatment effect for people over 75 years was consistent with expert opinion that people in earlier disease stages may have a larger treatment effect (see section 3.6). The company explained that the results should be interpreted with caution because of small patient numbers in each subgroup. The clinical experts explained that the result might be because there is a larger proportion of people who are homozygous or heterozygous for APOE4 in the younger age categories. This is expected because being homozygous or heterozygous for APOE4 increases the risk of having Alzheimer's disease at a younger age. The committee noted that age was not a stratification variable, meaning that there could have been imbalances in effect modifiers in the subgroups by age. The company gave additional detailed explanations for the subgroup results that were confidential and cannot be reported here. The committee concluded that it was unable to draw meaningful conclusions from the subgroup results by age. This was because of the lack of statistical significance and power, and small sample sizes. But, it noted that there may be different treatment effects in people who are homozygous or heterozygous for APOE4. It recalled its earlier conclusion (see section 3.6) that it would like to see the distribution of the CDR-SB treatment effect. The committee noted that because age is a protected characteristic, it would need to be very certain that any recommendations based on age were appropriate. Because of the limitations of the subgroup analyses, and because the experts have outlined that lecanemab leads to clinical benefit for people of all ages, it concluded that it did not have this certainty.

Economic model

Company's model structure

3.10 The company developed a Markov model with 5 mutually exclusive health states to estimate the cost effectiveness of lecanemab compared with

placebo. The states were MCI caused by Alzheimer's disease, mild dementia caused by Alzheimer's disease, moderate dementia caused by Alzheimer's disease, severe dementia caused by Alzheimer's disease and death. People were modelled to move between all health states besides the death state, which was absorbing. The model had a monthly cycle length and a lifetime time horizon. Health-state membership of people in the model was derived using cohort simulation in discrete time. Two separate but identical health-state structures were used for people in the community setting and people in residential care. People were modelled to start in the community setting and could then move to residential care, but could not move back to community care once in residential care. The committee considered whether it would be preferable for a patient-level simulation model to be developed. It noted that such an approach may have been better suited to reflect the potential importance of patient heterogeneity on the treatment effect. But the extent to which this is important for cost-effectiveness results is not clear. The committee concluded that the company's model structure reflected health states relevant to the decision problem and natural history of Alzheimer's disease. It concluded that the model structure was acceptable for decision making, taking into account the uncertainty outlined above.

Transitions to better health states

3.11 In the company's model, most people were assumed to progress to worse health states over time. But, it allowed a proportion of the cohort to transition to better health states. For example, transition from the mild dementia caused by Alzheimer's disease health state to the MCI caused by Alzheimer's disease health state was possible. The EAG questioned the clinical validity of this assumption because the clinical experts said that Alzheimer's disease is a progressive disease. Also, lecanemab slows progression to more severe health states, rather than reversing progression. The EAG shared a scenario analysis that removed transitions to better health states, which substantially increased the incremental cost-effectiveness ratio (ICER). The company explained that

its approach was consistent with observed trial data, literature and expert opinion. It also noted that temporary improvements in the condition were seen in patient-level longitudinal data from the National Alzheimer's Coordinating Center (NACC, see section 3.12). It added that the model had a short monthly cycle length and movements to improved health states were temporary. It emphasised that the proportion of people who backwards transitioned to better health states was very small and for a short period of time. The clinical experts explained that it was possible for rare and short periods of improvement to occur. But overall people with Alzheimer's disease will progress to more severe disease over time. The committee noted that Alzheimer's disease is progressive. It thought that the observed changes may be because of measurement variability in clinician-reported CDR-SB or normal variability in a person's condition, rather than a reversal of the condition. It noted that including backward transitions was less important than accurate health-state occupancy generated in the model when compared with the trial. The committee concluded that the company's approach to modelling backward transitions was appropriate because the overall direction for people was disease progression.

Constant transition probabilities

3.12 The company's model assumed that transition probabilities were constant (did not change over time) for the time horizon of the model. For the first 18 months, it used transition probabilities estimated from Clarity AD data for both lecanemab and placebo. After 18 months, it based transition probabilities on Potashman et al. (2021) for placebo. This study used NACC data to estimate progression rates for people with confirmed amyloid at different stages of Alzheimer's disease. For lecanemab, it used a hazard ratio for a treatment effect of 0.69 from Clarity AD applied to placebo transition probabilities from Potashman et al. The company updated the hazard ratio before the committee meeting, but considered this to be commercial in confidence. The company thought that Clarity AD data from 18 months covered too short a time period to extrapolate over a

lifetime time horizon. It resulted in transitions that were not aligned with the underlying risk and natural history of Alzheimer's disease. The EAG questioned the validity of the company's approach because the Clarity AD data showed increases in people moving between health states over time. Increases over time would not be captured with constant transition probabilities. The company carried out multistate survival analysis on Clarity AD data to estimate transition probabilities that changed over time for the first 18 months in the model. It did not use the estimates in its base case. The EAG noted that the results suggested time-dependent transitions may be suitable and should be explored further. The committee concluded that it had not been presented with enough information to make a conclusion on the suitability of constant transition probabilities. It thought that the model outcomes must accurately reflect the trial data. But it needed to see further information on the alternative methods explored to determine whether constant transition probabilities would be suitable.

Face validity of transition probabilities

3.13 At clarification, the EAG raised that the company did not follow the tutorial by Gidwani et al. (2020) to derive transition probabilities. This approach is recommended for multiple health states and their conversion to a different period length matching the cycle length. The risk of not following the tutorial is significant errors in calculating the numbers of patients in each health state because of competing risks. The company made attempts to use the tutorials but ultimately thought that the outputs were not appropriate. The EAG noted that it would like to see the first solution proposed by Gidwani et al. (revising the model structure so that each node only has 2 model transitions) explored further. It also compared the results of the multistate survival analysis (see section 3.12) with constant transition probabilities to the company's base-case transition probabilities. Results showed large discrepancies, suggesting the original transition probabilities may not have been appropriate. The company also shared health-state occupancy figures at 18 months for each health state from Clarity AD data and the model. The figures are confidential and cannot be

reported here. It said that the results showed that the model accurately reflects state occupancy in Clarity AD for both lecanemab and placebo, despite minor differences. The EAG disagreed, noting that it did not consider the difference in modelled and trial state occupancy as minor. It claimed that it was clear that the model systematically overestimated the benefits of lecanemab. The EAG explained that roughly half of the modelled QALY gain in the company's base case was because of survival gains. The committee asked the clinical experts whether this was to be expected. They explained that a survival benefit with lecanemab was plausible because mortality increases as dementia progresses. So, lecanemab could increase survival if people spent more time in the MCI health state before progressing to dementia. But, the clinical experts noted that it was not possible to quantify the size of any survival benefit. The committee noted that it had not been presented with enough information to have confidence in the face validity of the transition probabilities in the model. It noted that the multistate survival approach may provide results with better face validity, and would like to see this explored further. The committee concluded that it would like to see transition probabilities used that lead to outcomes and mortality benefit consistent with trial data and clinical expectations. To verify this, it concluded that it would like to see disaggregated, discounted and undiscounted results for the company's and EAG's base cases, by modelled health states. It would also like to see scenario analyses in which the model structure is revised so that each node only has 2 model transitions, to align with the first solution proposed by Gidwani et al.

Stopping rules

3.14 Clarity AD did not include a treatment stopping rule for lecanemab. But, the company's base case included stopping rules for lecanemab. The first assumed that people stopped treatment once they enter residential care. The company explained that this stopping rule was based on feedback from UK clinical experts. The clinical experts in the committee meeting explained that some people move to residential care because of disease

progression. But, some people move to residential care for different reasons, for example, because of their carers' capacity. So, they thought that they would not want to apply a stopping rule based on entry to residential care in clinical practice. The committee also noted that applying a stopping rule based on entry to residential care could lead to increasing health inequalities. So, the committee concluded that it was not appropriate to apply a stopping rule based on entry to residential care. The second stopping rule assumed that people stop treatment once their condition has progressed to moderate dementia caused by Alzheimer's disease. This is aligned with the marketing authorisation for lecanemab. The clinical experts thought that it would be reasonable to stop treatment on progression to moderate dementia caused by Alzheimer's disease. But, they noted that there are no clear guidelines on how progression to moderate disease is defined (see section 3.2). The committee concluded that it wanted to see more information from the company on how the stopping rule would be applied in practice. For example, what measures would be used to determine progression and how often people would be assessed for progression. It also wanted clarification that the resource impact of implementing this stopping rule in the NHS had been adequately included in the modelling, for example, through sufficient follow-up appointments on lecanemab to assess disease progression.

Treatment discontinuation

3.15 The company's model assumed that all-cause treatment discontinuation was constant over time and derived from Clarity AD data. The model also assumed that people who stopped treatment in the MCI and mild dementia caused by Alzheimer's disease health states because of all-cause discontinuation (and not because of a stopping rule, see section 3.14) did not lose treatment effect. It justified this approach because the Clarity AD data used in the model (and the hazard ratio applied to Potashman et al. (2021) transition probabilities; see section 3.12) related to the intention-to-treat population, so discontinuations were accounted for in the efficacy data. It also assumed

that there was no waning of treatment effect while on treatment. But it assumed some treatment-effect waning when treatment was stopped because of progression to moderate or severe dementia caused by Alzheimer's disease. The exact figure is considered confidential by the company and can't be reported here. The EAG thought that it was unsuitable to assume a persistent treatment effect for people who stopped treatment in the MCI and mild dementia caused by Alzheimer's disease health states. So, it removed this assumption in its base case. Instead, it assumed that people who stopped lecanemab had no further treatment effect after stopping. It also noted that it was unclear whether it was appropriate to assume a constant rate of stopping from Clarity AD after 18 months. The EAG explained that it would be useful to see treatment waning scenarios after stopping lecanemab in the MCI and mild dementia caused by Alzheimer's disease health states. The clinical experts noted that it is highly implausible that a person's condition will immediately worsen after stopping treatment with lecanemab. They added that amyloid levels do not suddenly revert to baseline levels on stopping treatment. The company estimated the rate at which amyloid reaccumulates, but considers this information confidential, so it cannot be reported here. But, the clinical experts noted that the relationship between level of amyloid plaques and symptoms of Alzheimer's disease is unclear. The committee concluded that it was inappropriate to assume that people who stopped treatment in the MCI and mild dementia caused by Alzheimer's disease health states continued to have the same treatment benefits as people who remained on treatment. But it had not been presented with any scenarios that explored treatment-effect waning. So, its preference in the absence of any other scenarios was to assume that people who stopped treatment stopped having treatment benefits. It concluded that it would like to see alternative treatment-effect waning scenarios. It also concluded that it would like to see scenarios varying the all-cause discontinuation rate after 18 months.

Utility values

Utility values used in the model

3.16 The company's original base-case model included utility values for people with Alzheimer's disease and their carers. EQ-5D values reported by people with Alzheimer's disease were used for MCI and mild dementia caused by Alzheimer's disease health states. Proxy-reported estimates were used for moderate and severe dementia caused by Alzheimer's disease health states. The company highlighted that this approach was agreed with clinical experts because people with more advanced Alzheimer's disease may be unable to accurately respond to quality-of-life questions. Utility values for carers were taken from the literature and modelled as a function of the health state of the person with Alzheimer's disease. Utility values for people with Alzheimer's disease and carers were also adjusted when a person with Alzheimer's disease entered residential care. This included a disutility of 0.09 for carers. Utility impacts from adverse events were not modelled. The company explained that the associated disutility would be captured in EQ-5D data from the trial. The EAG raised several concerns with the utility values used in the company's model. They were:

- Utility values for the MCI and mild dementia caused by Alzheimer's disease health states used mean EQ-5D values, which did not consider variation between people, potential confounding variables and changes to utility over time.
- Utility values were treatment dependent (meaning people have different utility values for lecanemab and placebo, despite being in the same health state), which could not be reasonably justified within the current approach.
- Utility values for the MCI and mild dementia caused by Alzheimer's disease health states were higher than the UK age and gender matched general population utilities, which lacked face validity.

- It was unclear whether it was appropriate to assume additional disutility for caregivers when a person with Alzheimer's disease entered residential care.
- It was inappropriate to assume that the disutility of adverse events was already captured in Clarity AD data because quality-of-life data was collected in 6-monthly intervals. Adverse events were likely to have occurred and resolved in that time, so not be reflected in the data.

So, the company submitted an updated base case that used a mixed effects model with repeated measures with backward elimination. This was done to address the EAG's concerns around using mean EQ-5D values. But, the company used proxy-reported estimates for all health states because the estimates for patient-reported utilities were inconsistent. The EAG was unable to critique the new approach adopted by the company because it was received shortly before the committee meeting. But it noted uncertainty with using proxy-reported utility values for all health states. The company justified using treatment-dependent utilities, saying that it reflected the trial data. It added that the difference between lecanemab and placebo arms may have been attributable to differences in disease severity. For example, a CDR-SB score of 5 and 9 would both be classified as mild Alzheimer's disease, despite the former potentially being expected to have more favourable utilities. The company also updated its base case to include disutility for serious and severe adverse events. The EAG commented that this change only partially resolved its concerns. This was because lower grade adverse events were not modelled and the durations of adverse events that were modelled may have been too short. So, the EAG was still concerned that disutility from adverse events was underestimated. The committee concluded that the company's approach to modelling utility values was not clear. It noted the efforts of the company to address the EAG's concerns. But, it thought that this led to a lack of clarity on the final approach of the company and the justification for this. It was also aware that the new base case had not been fully critiqued by the EAG. So, the committee

concluded that it would like to see a detailed outline of the utility values used for each health state, the data source for them and justification for that source. It would also like to see a complete EAG critique of the final approach. The committee noted that the NICE manual for health technology evaluations states that health-related quality of life should be measured directly by people with the condition being treated. But, when it is not possible to get these measurements directly from such people, they should come from people acting as their carers. It understood that people with Alzheimer's disease may be unable to complete quality-of-life questionnaires because of cognitive decline, and that it may be suitable to use proxy measures. But, it noted there was evidence that there was poor agreement between quality of life estimated by people with Alzheimer's disease and by carer proxy. The committee also noted concerns that self-reported quality of life may not be an accurate reflection of quality of life because people adapt to the symptoms of their condition. So, they are not recording their quality of life relative to true perfect health. The committee concluded that it would like to see further information from the company on its approaches to utility values, taking into account these concerns. This should include further justification on the use of proxy values, with reference to the available literature.

Costs

Infusion costs

3.17 The company's model assumed that the administration cost of each lecanemab infusion was £208. This was based on the SB12Z tariff cost in the 2021/2022 National Tariff Payment System, uplifted to reflect current prices. The code relates to a simple parenteral chemotherapy at first infusion. The company explained that this code was the most appropriate for estimating lecanemab infusion costs in the absence of an exact infusion cost estimate for lecanemab for Alzheimer's disease. This was because lecanemab is given over a 1-hour infusion, alongside about 30 minutes of nurse time. Submissions from NHS England identified a

different cost that it thought were most suitable. This was £565, based on the WD02Z healthcare resource group (HRG) code estimate from 2019/2020 and uplifted to current prices. The code is titled 'Alzheimer's Disease or Dementia, treated by a Non-Specialist Mental Health Service Provider'. NHS England explained that this is the HRG code that would most likely be recorded when a person has a lecanemab infusion. It reflects the actual amount that service providers will currently be paid to provide a lecanemab infusion. NHS England explained that the cost it calculated may be conservative because there is no single published price, so it used the average across multiple indications, not just for Alzheimer's disease, which is a higher cost. The clinical experts explained that they would expect the infusion cost to be close to the £208 value suggested by the company. Their experience of lecanemab was that of a similar infusion time and monitoring to that of chemotherapy treatments. NHS England explained that the cost it preferred includes administration of a monoclonal antibody, which may need more intensive monitoring and nursing time than chemotherapy. The patient and clinical experts added that the infusion of lecanemab is not complex and does not need intensive monitoring. The committee concluded that the wide variation in the infusion costs estimated by the company and NHS England had not been sufficiently explained. So, it was unable to determine a preferred cost for use in modelling. It concluded that it would like to see further information, including a breakdown of expected resource use, from the company and NHS England that fully explained the estimated costs and explored alternatives.

Private care costs

3.18 The company's submission included an estimate of direct non-medical costs to account for social care costs, such as residential care and home-based community care costs. It used costs estimated by Alzheimer's Society research in 2014, and adjusted them to reflect current prices. At clarification, the EAG questioned what proportion of the estimated costs related to private care and so would be outside of the cost perspective set

out in the NICE reference case. The company's response was that the costs did include private care costs but the proportion was not identified by the authors. It provided a scenario analysis that assumed an arbitrary 10% of the costs were private and so excluded. The EAG noted that, elsewhere, the Alzheimer's Society had estimated that two-thirds of annual dementia costs are currently paid by people with dementia and their families. This is either in unpaid care or in paying for private social care. So, the EAG provided a scenario that assumed two-thirds of the costs used by the company were paid for privately and so excluded. But, it noted that the estimate was likely to be too high because the cost used by the company did not include unpaid care. The committee concluded that it was unclear what proportion of the costs used by the company could be attributed to private costs and so excluded. It noted that it would like to see further justification for the appropriate proportion of the costs assumed be for private care. This could include, for example, justification from the authors of the study cited by the company on the breakdown of costs, or an alternative estimate of direct non-medical costs.

Amyloid beta testing costs

3.19 Treatment with lecanemab is conditional on confirmed amyloid beta pathology. So, the company included the diagnostic testing costs in its base case. It did this by assuming that 90% of people will be tested using cerebral spinal fluid (lumbar puncture) and 10% will be tested using a PET-CT scan. The company also included costs for people who are tested but do not have lecanemab. It assumed 28.8% of people tested would not be eligible, based on screening in Clarity AD. The EAG's clinical expert agreed that 90% of people will be tested using a lumbar puncture and 10% of people will be testing using a PET-CT scan. But, the EAG used a higher screening failure rate of 43.1% in its base case. This was based on a report by the NICE Health Technology Assessment lab that estimated the eligible population for lecanemab. The clinical experts indicated that they would expect a screening failure rate of about 20% in NHS clinical practice. NHS England agreed, explaining that it used a

screening failure rate of 20% in its eligible population calculations. The committee concluded that it was appropriate for the company to assume that 90% of people tested for amyloid beta will have a lumbar puncture and 10% will have a PET-CT scan. It also concluded that it was appropriate to assume that 28.8% of people who are tested for amyloid beta will not have amyloid pathology, so will not be eligible for lecanemab.

Severity

3.20 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE manual for health technology evaluations. But the values did not meet the threshold for a severity weight greater than 1 to be applied to the QALYs. The committee recalled the powerful testimony from patient experts and considered the significant impact of Alzheimer's disease on people with the condition and their carers. But, the committee recalled that the absolute and proportional QALY shortfall thresholds were not met in the company's and EAG's base cases. So, it concluded it should not apply a greater weight to QALYs.

Cost-effectiveness estimates

Committee's preferred assumptions

3.21 The committee concluded that the cost-effectiveness estimates were very uncertain, and that further analyses were needed (see section 3.22). But the committee concluded that it could state some preferred assumptions for the cost-effectiveness modelling for lecanemab compared with placebo based on current modelling:

- The company's overall model structure was acceptable for decision making (see section 3.10).

- The company's approach to modelling backward transitions was appropriate because the overall direction for people was disease progression (see section 3.11).
- Ninety per cent of people tested for amyloid beta have a lumbar puncture and 10% have a PET-CT scan, and 28.8% of people who are tested for amyloid beta will not have amyloid pathology (see section 3.19).

Uncertainty in the cost-effectiveness estimates

3.22 The committee recalled the uncertainties in the lack of long-term evidence for lecanemab and the company's modelling assumptions. It thought that there remained substantial uncertainty in the cost-effectiveness estimates generated using its preferred assumptions because of uncertainty:

- in the face validity of transition probabilities
- on the impact of treatment discontinuation on outcomes
- on how the stopping rule for lecanemab would be applied in practice, and the impact on costs and outcomes
- in utility values used in the model
- in infusion, testing and private care costs.

The committee thought that it would like to see the following analyses and further evidence to enable it to decide on the cost effectiveness of lecanemab:

- the distribution of change from baseline in CDR-SB score at 18 months, compared for lecanemab and placebo arms (see section 3.6)
- the mean difference from baseline by treatment arm at 18 months for the 6 individual domains of CDR-SB (see section 3.6)
- the least-squares mean change from baseline in EQ-5D-5L utility values, by treatment arm, analysed using a mixed effects model with repeated measures (see section 3.6)

- further information from clinical experts on what the introduction of lecanemab would do to the proportion of people who have MCI or mild dementia caused by Alzheimer's disease (see section 3.8)
- the distribution of the CDR-SB treatment effect for different subgroups that may have different treatment effects (see section 3.9)
- further information on the justification of constant transition probabilities and other approaches explored (see section 3.12)
- transition probabilities in the model that lead to outcomes and mortality benefit consistent with trial data and clinical expectations (see section 3.13)
- a scenario analysis in which the model structure is revised so that each node only has 2 model transitions, to align with the first solution proposed by Gidwani et al. 2020 (see section 3.13)
- disaggregated, discounted and undiscounted results for the company's and EAG's base cases, by modelled health states (see section 3.13)
- more information from the company on how the stopping rule on progression to moderate Alzheimer's disease would be applied in practice, including what measure would be used to determine progression and how often people would be assessed for progression (see section 3.14)
- justification of how the stopping rule had been included in the modelling (see section 3.14)
- scenarios exploring treatment waning for people who stop treatment because of all-cause discontinuation (see section 3.15)
- scenarios exploring varying assumptions for the rate of all-cause discontinuation after 18 months (see section 3.15)
- detailed outline of the utility values used for each health state for both people with Alzheimer's disease and their carers, the data source for them and justification for that source, including considerations of proxy utility values and adaptation by people with Alzheimer's disease (see section 3.16)

- a complete EAG critique of the final approach to model utility and disutility values (see section 3.16)
- further information from the company and NHS England that fully explains estimated infusion costs and explores alternatives (see section 3.17)
- further information from the authors of the Alzheimer's Society report used to estimate direct non-medical costs on the proportion of costs that are private, or an alternative estimate of direct non-medical costs (see section 3.18).

Company and EAG cost-effectiveness estimates

3.23 The cost-effectiveness results included confidential prices for lecanemab, so the exact results cannot be reported here. The company's deterministic base-case ICER for lecanemab compared with placebo was considerably above the range normally considered cost effective for routine NHS use. Also, the EAG's corresponding base-case ICER was significantly higher than the range normally considered cost effective. Cost-effectiveness estimates by APOE4 subgroups (non-carriers, heterozygote carriers and homozygote carriers) in the company's and EAG's base cases were also considerably above the range normally considered cost effective. The committee noted that, in both the company's and EAG's base cases, the estimated QALY gains were small but incremental costs were large. It also noted that administration costs contributed to a large proportion of incremental costs, particularly in the EAG's base case (see section 3.17). The committee concluded that it could not recommend lecanemab for routine use. This was because, given the company's and EAG's base-case ICERs, the most plausible ICER was likely considerably above the range normally considered cost effective, and because of the uncertainty in all the cost-effectiveness estimates.

Managed access

3.24 Having concluded that lecanemab could not be recommended for routine use, the committee then considered whether it could be recommended

with managed access for treating MCI and mild dementia caused by Alzheimer's disease. The company proposed that data could be collected from the open-label extension of Clarity AD. The clinical lead for the Innovative Medicines Fund highlighted that the usefulness of data from the trial extension in resolving key uncertainties would be limited because there was no control arm. They also thought that there were considerable uncertainties that may not be addressed by further data collection. The committee also noted the views of the managed access team that the data collection proposed by the company did not have a high likelihood of addressing any key uncertainties. The committee recalled that it had not been presented with any cost-effectiveness results that suggested lecanemab had the plausible potential to be cost effective. So, the committee concluded that lecanemab did not meet the criteria to be considered for a recommendation with managed access. But, it would welcome an updated managed access proposal from the company that included further data collection and plausibly cost-effective ICERs.

Other factors

Equality and health inequality issues

3.25 Submissions from the company and experts identified potential equality and health inequality concerns for consideration. The issues identified were:

- There is current inequality in terms of who has an Alzheimer's disease diagnosis and accessing care. This will be exacerbated by introducing the complex diagnostic pathway for lecanemab.
- People with Down's syndrome (who have a more than 90% lifetime risk of developing Alzheimer's disease), people with young-onset dementia and people from diverse family backgrounds were not fully represented in Clarity AD. These groups are at risk of being excluded from accessing lecanemab.

- Lecanemab may have different treatment effectiveness and benefits for different subgroups based on age, sex and family background.
- Lecanemab would need significant increases in NHS capacity for service delivery. Inequalities may increase as existing services that are already under strain would be needed to deliver the treatment.

The committee noted the concerns raised with getting a diagnosis, accessing care in a new and complex pathway, and substantial demand on NHS services. It understood these concerns but noted that they were outside of its remit. The committee understood that some people with Alzheimer's disease have Down's syndrome and may be considered disabled under the Equality Act 2010. It also noted the possibility of different treatment effects for subgroups. Age, sex, family background and disability are protected characteristics under the Equality Act 2010. The committee agreed that any recommendation should not restrict access to treatment for some people over others on the basis of protected characteristics.

Uncaptured aspects

3.26 Stakeholder submissions throughout the appraisal identified potential uncaptured benefits and costs of lecanemab. The potential uncaptured benefits of lecanemab raised were:

- Utility values may have been underestimated by using patient-by-proxy-reported quality-of-life data.
- The impact on the finances and productivity of carers for people with Alzheimer's disease were not captured in the model. The committee noted that these costs fall outside of the NICE reference case.
- Lecanemab is innovative, as shown by its designation to the Innovative Licensing and Access Pathway by the Medicine and Healthcare products Regulatory Agency.
- Lecanemab was penalised by the 'carer QALY trap'. This was because caregiving costs and disutility were applied for longer for the carers of

people having lecanemab compared with placebo, given that people having treatment would live longer.

- Lecanemab is not eligible for the severity modifier despite:
  - Alzheimer's disease being the leading cause of death in the UK
  - the condition causing a significant disease burden
  - clinical consensus that treating milder Alzheimer's disease states is more beneficial than treating more severe disease states.

The potential uncaptured costs of lecanemab raised were:

- false hope for people who are not eligible for lecanemab, or who may find out they are APOE4 carriers and may experience worse outcomes than others
- false hope for people who believe that lecanemab is a cure for Alzheimer's disease and not a treatment that slows disease progression
- harmful effects of repeated diagnostic testing and monitoring
- significant increase in demand for NHS primary and secondary care services that may affect the provision of other services
- substantial investment in infrastructure and training for NHS care pathways to be redesigned to accommodate new treatments.

The committee concluded that the uncaptured benefits and costs of lecanemab may increase or decrease the most plausible ICER. But, it thought that there were significant uncertainties in the company's base case (see section 3.22). So, the committee was unable to reach a conclusion on the impact of uncaptured benefits and costs.

Conclusion

Recommendation

3.27 The committee recalled the high uncertainty associated with the company's model and long-term evidence for lecanemab. It thought that more evidence was needed to generate robust cost-effectiveness

estimates. It recalled that the EAG's and company's base cases were associated with uncertainty, and that the cost-effectiveness estimates were above the range normally considered a cost-effective use of NHS resources. So, it did not recommend lecanemab for treating MCI and mild dementia due to Alzheimer's disease in adults who are APOE4 heterozygotes or non-carriers, either for routine NHS use or with managed access.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Megan John

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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