Alzheimer Europe

Changing perceptions, policy and practice to improve the lives of people affected by dementia

Alzheimer Europe response on the negative CHMP opinion on lecanemab

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Background

Dementia affects almost 8 million people in the European Union, with numbers projected to double by 2050. As the most common cause of dementia by far, Alzheimer's disease (AD) has been a major focus of research efforts to identify new treatments. Recent clinical trials of anti-amyloid therapies have marked a turning point for the field, demonstrating a statistically significant slowing of clinical decline for participants receiving treatment, compared to those receiving a placebo.

Based on the positive results of the Clarity AD Phase 3 clinical trial of lecanemab, manufacturer Eisai submitted a marketing authorisation application for the drug to the European Medicines Agency (EMA) in January 2023. On 26 July 2024, the EMA's Committee for Medicinal Products for Human use (CHMP) issued a negative opinion on the marketing authorisation application of Eisai for lecanemab, for the treatment of early Alzheimer's disease (defined as mild cognitive impairment or mild dementia due to Alzheimer's disease).

In its opinion, the CHMP identified the risk of amyloid-related imaging abnormalities (also known as ARIA) as a major issue. In particular, the CHMP was concerned by the elevated risk of ARIA in people with two copies of the Apo-Eε4 gene. The CHMP concluded that the benefits of lecanemab in slowing cognitive decline did not outweigh the risks of serious adverse events.

On 5 August, Eisai requested a re-examination of the negative opinion for lecanemab. Following receipt of the grounds for Eisai's request, the CHMP will have 60 days to re-examine their opinion, and a final outcome is expected by the end of 2024.

Alzheimer Europe's concerns about the negative opinion of the CHMP

Alzheimer Europe regrets the negative opinion from the CHMP and hopes that the re-examination will result in a decision that will allow people with early AD in the European Union, Iceland, Liechtenstein and Norway to access treatment options available in other countries, with stringent eligibility criteria and efficient monitoring of side effects to ensure patient safety .

This response to the CHMP opinion identifies six key areas of concern for Alzheimer Europe and its member organisations.

1. Excluding European patients from treatments available in other countries risks exacerbating inequity

At the time of writing, eight global regulators have approved lecanemab. The US Food and Drug Administration (FDA) granted traditional approval to lecanemab in July 2023, after unanimous endorsement of its clinical efficacy by an advisory committee. Similar approvals were adopted in Japan (25 September 2023), China (3 January), South Korea (27 May), Hong Kong (11 July), Israel (12 July), the United Arab Emirates (13 August) and the United Kingdom (22 August).

The CHMP opinion is at odds with the decisions by regulatory authorities in these countries. Alzheimer Europe supports the independent assessment of medicines across regions and values the EMA's scientific rigour. However, it is difficult to understand the CHMP's negative decision on a drug which has been approved by eight other regulators to date.

As a result of these inequalities in access to treatments, wealthier patients may seek treatment abroad, a choice unavailable to those with lower incomes or from marginalised groups.

A negative decision, which deprives European patients from accessing a new treatment that is available in many other countries, therefore risks creating disparities, and worsening health inequalities.

2. Excluding all patients from anti-amyloid treatments restricts patients' autonomy and reduces choice

Patients and their families deserve the right to engage in discussions with their physicians and make informed choices about treatments, based on their individual circumstances, preferences and values, including the acceptability of risk and anticipated benefits. The refusal of lecanemab would prevent this engagement and shared decision making between patients, their families and their physicians, thus raising ethical concerns about the balance between regulatory caution in excluding all patients from new treatments, and the right of individuals to choose and make risk-benefit decisions .

A negative decision would therefore undermine patient autonomy, restricting clinicians from offering a disease-modifying treatment for AD to patients who could make their decision based on their own assessment of possible risks and benefits.

3. Risk management approaches are feasible and available to determine eligibility for anti-amyloid treatments and monitor of side effects

Alzheimer Europe welcomes the approach by the CHMP to highlight the safety concerns for anti-amyloid treatments and especially the elevated risk of ARIA in people with two copies of the ApoEε4 gene.

A number of regulatory authorities that have approved lecanemab shared these safety concerns and have therefore incorporated robust risk management measures, including post-authorisation safety studies and controlled access programmes that exclude high-risk patients. Regulators have also mandated MRI scans before starting treatment, requiring regular MRI monitoring for ARIA during the first 6 months of treatment. Together, these approaches help address concerns about ARIA, ensuring that lecanemab can be administered safely. For example, the UK's Medicines and Healthcare products Regulatory Agency has excluded individuals carrying two copies of the ApoEε4 gene, which places them at substantially higher risk of ARIA, and requires MRI monitoring prior to the 5th, 7th and 14th infusions.

These risk management measures recognise the importance of balancing access to innovative treatments with rigorous safety oversight. They preserve the opportunity for access to a disease-modifying treatment for AD, ensuring that those who may benefit most are not unduly denied treatment options, whilst protecting individuals who are at greatest risk of ARIA and other side-effects. In addition, post-authorisation safety studies provide valuable information on the real-world outcomes of patients receiving treatment, allowing for ongoing evaluation and refinement of innovative therapies.

4. These medicines can provide meaningful benefits to patients and carers by also positively impacting quality of life and caregiver burden

Clarity AD was an 18-month, double-blinded, placebo-controlled phase 3 clinical trial which examined the safety and efficacy of lecanemab for the treatment of early AD. The trial met all its primary and secondary endpoints, showing modest but statistically significant reductions in clinical decline on scales such as CDR-SB and ADAS-Cog14, which are clinician-reported scales that measure cognition and function.

While these scales are undoubtedly important for the clinical assessment of efficacy, health outcome measures that assess quality of life and caregiver burden are often deemed to be more meaningful for patients and carers. In Clarity AD, lecanemab treatment was associated with a preservation of health-related quality of life, as measured on the EQ-5D-5L and QOL-AD scales. Approximately 50% slower decline was observed across items such as ability to do chores, anxiety/depression, and interactions with family & friends in the patient-reported elements of these scales. 38% less decline was observed on scales measuring caregiver burden, reported by study partners of participants receiving lecanemab.

5. The availability of disease-modifying treatments will support the development of patient pathways promoting timely diagnosis and access to disease management and support

In our 2024 Position Paper on anti-amyloid therapies for AD, we highlighted the importance of equitable access to a timely and accurate AD diagnosis, allowing people with AD to access treatments, support and care. A timely diagnosis of early AD has a number of benefits beyond eligibility for treatment with anti-amyloid drugs. Early detection and diagnosis of AD is instrumental in enabling patients and their loved ones to plan for the future. Having a confirmed diagnosis is also the first step towards accessing support services and care pathways, where available.

The availability of anti-amyloid therapies will incentivise healthcare systems to adapt, to promote access to innovative therapies and create processes for patients to receive timely diagnoses and patient-centred care. According to US-based clinicians, the availability of lecanemab has prompted improvements in patient pathways by encouraging earlier diagnosis of AD, which has led to a greater emphasis on biomarker testing and advanced diagnostic tools.

In the absence of an approved disease-modifying treatment for AD, European healthcare systems may have fewer incentives to adapt and improve, further disadvantaging people with AD and other forms of dementia in Europe.

6. Negative regulatory decisions may impact the overall attractiveness of Europe as a centre for research and development in the Alzheimer's field

The cost of AD drug development is high, and failures are relatively common. According to recent estimates, companies have invested over USD 40 billion in clinical research on AD since 1995. However, figures indicate that Europe may be falling behind in terms of R&D investment. An analysis of active Phase I, II and III trials that are currently recruiting participants found that more clinical trials are conducted in the US than any other global region, with 112 active AD trials. Although Europe remains an important region for clinical trials, there are fewer than 50 active AD trials that are currently recruiting participants in the EU.

There are many factors that impact decisions on R&D investment. Nevertheless, there is a risk that refusing the authorisation of disease-modifying treatments in Europe may impact the momentum of ongoing research into novel treatments for AD, prompting companies to deprioritise Europe as a location for clinical trials. This could lead to fewer opportunities for European AD patients to participate in clinical trials.

The way forward

Anti-amyloid drugs have the potential to change the course of a disease that is one of the leading causes of dependence and disability worldwide and the third cause of death in the WHO European Region.

Together with our 41 member associations, we therefore hope that European regulators and companies can arrive at a solution which will allow people with early AD in Europe to access anti-amyloid treatments available in other countries, with robust measures to ensure that those patients most at risk of serious side effects will be excluded from treatment.

Alzheimer Europe acknowledges the very real safety risks associated with treatment and would welcome a restriction to the indication of lecanemab to exclude those at greatest risk of ARIA, such as individuals carrying two copies of the ApoEε4 gene and those receiving treatment with anticoagulants.

Alzheimer Europe also calls on the CHMP to require drug manufacturers to develop risk management plans that include controlled access programmes, balancing access to innovative treatments with rigorous safety oversight. Moreover, Alzheimer Europe calls for the establishment of post-authorisation safety studies and patient registries for long-term collection of real-world evidence on lecanemab and other anti-amyloid drugs, including outcomes that are meaningful for patients and their carers.

Alzheimer Europe remains committed to a holistic approach to Alzheimer's disease and dementia, where innovative new treatments are included alongside counselling, support and adequate care of people with dementia and their carers throughout the disease process.

The organisation therefore reiterates its call for continued research into other treatment options, including symptomatic therapies and treatments for people in more advanced stages of dementia.

This position was adopted by the Alzheimer Europe Board on 30 September, 2024.

Declaration of interests: Alzheimer Europe had an audited income of EUR2,404,596 in 2023. Sponsorship by the developing companies of lecanemab (Eisai and Biogen) amounted to EUR 37,500 or 1.56% of total income. Sponsorship by pharmaceutical companies is only accepted in accordance with the organisation's Sponsorship guidelines and, in line with the European Medicines Agency criteria for patient organisations, declared in full transparency on the Alzheimer Europe website:

https://www.alzheimer-europe.org/about-us/governance/finances/alzheimer-europe-sponsors