Alzheimer Europe

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

AE position on EMA assessment of blarcamesine

Adopted by the AE Board on 16 March 2026

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Background

Dementia affects more than 9 million people in the European Union, with numbers projected to rise by nearly 60% 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.

Another experimental AD candidate drug, blarcamesine, which is an orally-administered small molecule, represents a different therapeutic approach compared to anti-amyloid antibodies, as a daily, oral medication that does not require intravenous infusions or brain scans for safety monitoring. Rather than targeting plaques directly, blarcamesine is designed to restore cellular homeostasis by activating the sigma-1 receptor (SIGMAR1), which promotes cellular homeostasis and autophagy, and thereby slow neurodegenerative processes upstream of amyloid and tau pathology.

Based on the results of the Phase Ib/III ANAVEX2-73-AD-004 trial, supported by longer-term follow-up in the open-label extension ATTENTION-AD study, Anavex Life Sciences submitted a marketing authorisation application for the drug to the European Medicines Agency (EMA) in November 2024. ANAVEX2-73-AD-004 was a randomised, placebo-controlled trial with 462 participants aged between 60 and 85, who received a once-daily oral dose of blarcamesine. On 11 December 2025, the EMA's Committee for Medicinal Products for Human use (CHMP) issued a negative opinion on the marketing authorisation application of Anavex for blarcamesine, for the treatment of early AD (defined as mild cognitive impairment or mild dementia due to AD).

The CHMP recommended refusal of the application on the basis that the main study failed to demonstrate effectiveness and safety of blarcamesine in people with early AD who do not have a mutation in the *SIGMAR1* gene. The CHMP noted methodological issues in the data which raised concerns about the validity of the results. The CHMP also noted that a high proportion of patients stopped treatment during the main study, mainly due to side effects related to the central nervous system (e.g. dizziness), which raised concerns about how well the medicine is tolerated.

On 17 December 2025, Anavex requested a re-examination of the negative opinion for blarcamesine.

Alzheimer Europe's response to the negative opinion of the CHMP

Alzheimer Europe understands the CHMP view that the provided efficacy and safety data may have been insufficient to recommend a full marketing authorisation for blarcamesine. However, the organisation would strongly support the granting of a conditional marketing authorisation with an obligation for the company to conduct an additional phase III clinical trial and to collect real world evidence from patients being treated in European countries.

Alzheimer Europe feels that the data provided by the company meets the requirements for such a conditional marketing authorisation, namely:

- the medicine fulfils an unmet medical need
- the benefit-risk balance of the medicine is positive,
- the company can be required to provide comprehensive data post-authorisation and
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data is still required.

Alzheimer Europe therefore hopes that the re-examination will result in a decision that will allow people with early AD in Europe to access another treatment option with stringent eligibility criteria and efficient monitoring of side effects to ensure patient safety.

This position statement, issued in response to the CHMP opinion, identifies the following key reasons for Alzheimer Europe and its member organisations to support a conditional approval of blarcamesine.

Alzheimer's disease remains an area of unmet medical need

AD continues to represent a significant unmet medical need in Europe, affecting over 7 million people in the EU alone.

Current medicines that are available and reimbursed in most European countries, such as donepezil and memantine can provide relief for certain symptoms in the mild and moderate dementia stages, but do not affect the underlying disease processes. In addition, these medicines are not indicated for people with mild cognitive impairment due to AD.

Anti-amyloid therapies have now received a marketing authorisation by the European Commission, but are currently only covered by national health systems in few EU countries. In addition, these treatments only benefit a small group of patients and require complex and costly administration and follow-up regimens. People with Alzheimer's disease with two copies of the ApoE4 gene are explicitly excluded from treatment according to the approval conditions in Europe, due to the higher risk of side effects such as amyloid-related imaging abnormalities (ARIA).

Blarcarmesine could offer a further treatment option for people with early AD, with an oral mode of administration as well as a risk profile that does not require extensive safety monitoring. Alongside donanemab and lecanemab, it could therefore support more personalised decision-making between patients, carers and doctors, taking into account individual risk factors, preferences and treatment needs.

Targeted risk management strategies could enhance the benefit-risk profile of blarcamesine

As with previous CHMP assessments, Alzheimer Europe welcomes the careful consideration of safety concerns in the evaluation of blarcamesine.

Although neurological side effects during the dose titration phase were relatively common in the main trial of blarcamesine, these were transient and predominantly of mild to moderate severity. Specifically, dizziness was reported in approximately 36 % of participants and confusional state in about 14 %.

Alzheimer Europe is encouraged by the fact that blarcamesine demonstrated a generally favourable safety profile with no associated ARIA. This absence of ARIA suggests that blarcamesine avoids the risks observed with treatments like lecanemab and donanemab, where ARIA-E (edema) and ARIA-H (microhemorrhages) have been reported and require safety monitoring. As a result, routine MRI monitoring may not be required. Given its differentiated mechanism of action and safety profile, oral blarcamesine could therefore represent a treatment option that is complementary to, or an alternative to, anti-amyloid therapies.

When it comes to the reported cases of dizziness, open label extension data indicated that a modified titration protocol could reduce the incidence of these side effects.

Blarcamesine can provide additional benefits in certain patient populations

Results of the ANAVEX2-73-AD-004 trial, which were published in a scientific journal in January 2025, showed that blarcamesine slowed clinical progression by 36.3% on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13) after 48 weeks of treatment, while the Alzheimer's Disease

Cooperative Study – Activities of Daily Living Scale (ADCS-ADL), the other co-primary endpoint measuring activities of daily living, did not reach statistical significance. Alzheimer Europe recognises that the study failed to meet its main objective, which was to show an improvement in both efficacy endpoints.

People receiving 30 or 50mg of blarcarmesine also showed 27.6% less decline in the study's secondary outcome, the Clinical Dementia Rating Scale Sums of Boxes (CDR-SB), along with improvements in key indicators of AD pathology, including an increase in plasma Aβ42/Aβ40 ratio and a reduction in brain volume loss.

Subgroup analyses based on absence or presence of the *SIGMAR1* gene variant were conducted to assess the impact of this genetic variant on clinical efficacy. These analyses suggested that treatment effects may be stronger in people without the *SIGMAR1* mutation. People without this mutation experienced 49.8% and 33.7% slower decline on the ADAS-Cog13 and CDR-SB respectively. These findings suggest that blarcamesine may provide greater clinical benefit in a genetically defined subgroup of people, representing a clinically meaningful benefit for a certain patient population.

In order to further improve the benefit/risk balance, the CHMP could therefore consider restricting the indication for blarcamesine to people who do not carry the *SIGMAR1* mutation.

Alzheimer Europe would support a restriction of the indication with the proposed changes in titration to improve side effects, which may improve the benefit-risk balance of blarcamesine and meet the requirements for the granting of a conditional marketing authorisation.

The way forward

Alzheimer Europe recognises the importance of a thorough and independent assessment by the European Medicines Agency and notes the lack of a pivotal Phase 3 clinical trial of blarcamesine.

The provided data indicate that a modified titration protocol could reduce the incidence of side effects, while restricting treatment to a genetically-defined subgroup of patients could improve the benefit-risk balance. We urge the CHMP, in its re-examination, to consider a conditional approval of the drug under a restricted indication alongside tight risk management measures, which would provide access to blarcamesine whilst enabling the collection of additional data.

In addition, the company should be required to conduct a phase III clinical trial to confirm these results and collect real world evidence of the safety and efficacy of these treatments in people with early AD in Europe.

As set out in Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use, the compliance of the company with the requirements of the conditional approval should be monitored strictly and the conditional approval should be turned into a full approval if the phase III data confirm the medicine's positive benefit/risk profile or revoked if the phase III data do not confirm this.

Alzheimer Europe also uses this statement to restate its commitment to a holistic approach to AD and dementia, where medicines 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. In this regard, Alzheimer Europe stresses the need for more research into primary and secondary prevention of dementia, as well as care and support for people living with the condition.

This position was adopted by the Alzheimer Europe Board on 16 March, 2026.

Declaration of interests: Alzheimer Europe had an audited income of EUR 3,142,316 in 2025. Sponsorship by the developing company of blarcamesine (Anavex) amounted to EUR 25,725 or 0.73% 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