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Update as of 10 April 2025:

The company for Kisunla has requested a re-examination of EMA's March 2025 opinion. Upon receipt of the grounds of this request, the Agency will re-examine its opinion and issue a final recommendation.

Refusal of the marketing authorisation for Kisunla (donanemab)

The European Medicines Agency has recommended the refusal of the marketing authorisation for Kisunla, a medicine intended for the treatment of early Alzheimer's disease.

The Agency issued its opinion on 27 March 2025. The company that applied for authorisation, Eli Lilly Nederland B.V., may ask for a re-examination of the opinion within 15 days of receiving the opinion.

What is Kisunla and what was it intended to be used for?

Kisunla was developed as a medicine to slow the progression of Alzheimer's disease in adults with amyloid beta plaques in the brain and mild cognitive impairment (memory and thinking problems) or mild dementia due to Alzheimer's disease (early symptomatic Alzheimer's disease).

During the procedure, the company proposed restricting the use of Kisunla to patients who do not have *ApoE4*, a gene for the protein apolipoprotein E. People who have one or two copies of this gene are at higher risk of developing serious side effects with medicines that work in the same way as Kisunla.

Kisunla contains the active substance donanemab and was to be given as an infusion (drip) into a vein once every 4 weeks.

How does Kisunla work?

The active substance in Kisunla, donanemab, is a monoclonal antibody (a type of protein) that attaches to a substance in the brain called amyloid beta. In people with Alzheimer's disease, the amyloid beta

[1] This Q&A was amended on 25 July 2025 to correct the change in iADRs score in patients who received Kisunla from 10 to 11 points

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forms plaques, which can lead to problems with brain function. By attaching to amyloid beta, the medicine was expected to reduce these plaques in the brain and slow the disease progression.

What did the company present to support its application?

The company provided data from a study involving 1,736 patients with early Alzheimer's disease who had amyloid beta plaques in their brain and who received either Kisunla or placebo (a dummy treatment). The study included patients both with and without copies of the *ApoE4* gene. The main measure of effectiveness was a change in symptoms after 76 weeks, measured using the integrated Alzheimer's disease rating scale (iADRs). The iADRs measures how much the disease affects a patient's cognitive ability and functional ability (their ability to carry out daily tasks). Scores on the iADRs range from 0 to 144, with lower scores indicating worse cognitive and functional ability.

What were the main reasons for refusing the marketing authorisation?

In the study, the most important safety concern with Kisunla was the frequent occurrence of amyloid-related imaging abnormalities (ARIA), a side effect known to occur with monoclonal antibody medicines that target amyloid beta. ARIA is seen with brain imaging and involves swelling and potential bleeding in the brain. ARIA occurred in 36.8% of people who received Kisunla compared with 14.9% of people who received placebo. Although most cases did not involve symptoms, 1.6% of people treated with Kisunla experienced serious ARIA events, which resulted in death in 3 cases.

Further analyses looked at the rates of ARIA in a smaller group of people with no copies of *ApoE4*, who are known to have a lower risk of developing this side effect. In this restricted population, ARIA occurred in 24.7% of people who received Kisunla compared with 12% of people who received placebo. Moreover, serious ARIA events, one of which led to death, still occurred in people treated with Kisunla (0.8%).

In terms of effectiveness, the study showed that, overall, the iADRs score worsened by 11 points in patients who received Kisunla and 13 points in those given placebo. In people who had no copies of *ApoE4*, these figures were 14 for patients receiving Kisunla and 16 for those receiving placebo. In addition, there were no long-term effectiveness data to support these results in patients without copies of the *ApoE4* gene.

The Agency noted that the benefits of Kisunla were not large enough to outweigh the risks of potentially fatal events due to ARIA, even in the small group of people who do not carry copies of *ApoE4*.

In reaching its conclusion, the Agency acknowledged the unmet medical need for treatment of Alzheimer's disease and took into consideration the views of patients and healthcare professionals who shared their needs and experiences related to living with or treating the condition. The Agency also considered the views of a scientific advisory group, which included experts such as neurologists and people living with the disease, as well as submissions from patient and healthcare professional organisations who shared their views on the unmet needs of people living with Alzheimer's disease.

The Agency's opinion was that the benefits of Kisunla in patients without *ApoE4* copies did not outweigh its risks, and it recommended refusing marketing authorisation.

Does this refusal affect patients in clinical trials?

The company informed the Agency that there are no consequences for patients in clinical trials with Kisunla.

If you are in a clinical trial or compassionate use programme and need more information about your treatment, speak with your clinical trial doctor.