14 November 2024
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Update as of 27 February 2025:

As part of its decision-making process, the European Commission asked the CHMP to consider information on the safety of Leqembi that became available after the adoption of the CHMP opinion in November 2024 and whether this would require an update of the opinion. The Commission also asked the CHMP to consider whether the wording of the risk minimisation measures in Annex II of the opinion was clear enough to ensure correct implementation.

The CHMP has now considered this request and concluded that its November opinion recommending the marketing authorisation of Leqembi does not need to be updated. EMA has provided a response to the European Commission which will now resume the decision-making process for Leqembi's marketing authorisation.

Approval of the marketing authorisation for Leqembi (lecanemab)

Re-examination leads to recommendation to approve

After re-examining its initial opinion, the European Medicines Agency has recommended approving the marketing authorisation for the medicine Leqembi for the treatment of early Alzheimer's disease.

The Agency had initially refused the application on 25 July 2024 for the use of Leqembi in adults with early Alzheimer's disease. After re-examination, on 14 November 2024 the Agency recommended that marketing authorisation could be granted for a restricted indication in adults with early Alzheimer's disease who have only 1 or no copy of a gene called apolipoprotein E4 (*ApoE4*).

The company that applied for authorisation of Leqembi is Eisai GmbH.

What is Leqembi and what is it to be used for?

Leqembi is a medicine for treating adults with mild cognitive impairment (memory and thinking problems) and mild dementia due to Alzheimer's disease (early Alzheimer's disease). It is for use in people who have only 1 or no copy of the *ApoE4* gene and who have amyloid beta plaques in the brain.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Leqembi contains the active substance lecanemab and is to be given as an infusion (drip) into a vein once every two weeks.

How does Leqembi work?

The active substance in Leqembi, lecanemab, is a monoclonal antibody (a type of protein) that attaches to a substance called amyloid beta, which forms plaques in the brains of people with Alzheimer's disease. By attaching to amyloid beta, the medicine reduces the amyloid plaques in the brain.

What did the company present to support its application?

The company presented results from a main study involving 1,795 people with early Alzheimer's disease who had amyloid beta plaques in the brain and who received either Leqembi or placebo (a dummy treatment). The main measure of effectiveness was a change in symptoms after 18 months, as measured using a dementia rating scale known as CDR-SB. The CDR-SB scale is used to assess the severity of Alzheimer's disease in patients. It includes questions that help determine how much the patient's daily life has been affected by cognitive impairment. The scale ranges from 0 to 18, with higher scores indicating greater impairment.

What were the main reasons for initially refusing the marketing authorisation?

In July 2024, EMA's human medicines committee, the CHMP, considered that the observed effect of Leqembi on delaying cognitive decline did not counterbalance the risk of serious side effects associated with the medicine.

The main study showed that after 18 months of treatment, the CDR-SB score in patients treated with Leqembi increased by 1.21 compared with 1.66 in those who received placebo. Although patients given Leqembi had lower CDR-SB scores than those given placebo, the difference between the two groups was small.

In terms of safety, the most important concern with Leqembi was the frequent occurrence of amyloid-related imaging abnormalities (ARIA), a side effect seen with brain imaging that involves swelling and potential bleeding in the brain. Although most cases of ARIA were not serious and did not involve symptoms, some patients had serious events. In addition, the risk of ARIA was more pronounced in people with *ApoE4*, particularly in those who had 2 copies of *ApoE4*.

Therefore, at the time of the initial refusal, the CHMP considered that the benefits of treatment were not large enough to outweigh the risks associated with Leqembi and recommended refusing marketing authorisation in the EU.

What happened during the re-examination?

During the re-examination, the CHMP re-assessed the data submitted by the company. The company proposed to restrict the use of Leqembi to patients with only 1 or no copy of *ApoE4* and provided additional analyses of data from the main study, which excluded data from 274 patients who carried 2 copies of the *ApoE4* gene and were therefore at highest risk of ARIA.

What were the conclusions of the re-examination?

The CHMP considered safety data related to two forms of ARIA, known as ARIA-E and ARIA-H. ARIA-E mainly involves accumulation of fluid in the brain and ARIA-H involves small bleeds. The results of these analyses showed that in patients treated with Leqembi, 8.9% of those with only 1 or no copy of *ApoE4* experienced ARIA-E, compared with 12.6% in all patients; similarly, 12.9% of patients in the restricted population experienced ARIA-H compared with 16.9% in the broader population.

In patients treated with placebo, the figures were 1.3% and 6.8% for ARIA-E and ARIA-H, respectively, in the restricted population.

In terms of effectiveness, the benefits of Leqembi in the restricted population are in line with those seen in the broader population. The data from the 1,521 patients with only 1 or no copy of *ApoE4* showed that, after 18 months of treatment, patients treated with Leqembi had a smaller increase in CDR-SB score than those who received placebo (1.22 versus 1.75), indicating slower cognitive decline. The results of other key measures indicated a similar effect to that seen in the CDR-SB score.

The CHMP concluded that the benefits of Leqembi outweigh the risks in patients with early Alzheimer's disease and 1 or no copy of *ApoE4*, provided that risk minimisation measures are in place to reduce the risk of severe and symptomatic ARIA and to monitor the consequences of ARIA in the long term. The Agency therefore recommended granting a marketing authorisation for Leqembi.

Leqembi will be available through a controlled access programme to ensure that the medicine is only used in the recommended patient population.

Patients will need to have MRI scans to monitor for ARIA before initiation of treatment and before the 5th, 7th and 14th dose of Leqembi. Additional MRI scans may be needed at any time during treatment if patients present with symptoms of ARIA (such as headache, confusion, visual changes, dizziness, nausea and difficulty walking). To increase awareness of ARIA and ensure early detection and treatment, the company will provide a guide and checklist for healthcare professionals, an alert card for patients and training programmes on ARIA for healthcare professionals. In addition, it must carry out a post-authorisation safety study to further characterise ARIA-E and ARIA-H and assess the effectiveness of the risk minimisation measures. The company will set up an EU-wide registry study of patients treated with Leqembi that can be used to estimate the incidence of side effects, including ARIA, and to determine how severe they are. The registry study can also be used to collect information about patients' progression to the next stages of Alzheimer's disease and the possible long-term consequences of ARIA.

During the re-examination the CHMP also considered submissions from patients, carers, clinicians and professional organisations, who shared their perspectives on the unmet needs of patients with Alzheimer's disease and the data on cognitive decline and risks.