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Refusal of the marketing authorisation for Leqembi (lecanemab)

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

The Agency issued its opinion on 25 July 2024. The company that applied for authorisation, Eisai GmbH, may ask for re-examination within 15 days of receiving the opinion.

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

Leqembi was developed as a medicine for treating adults with mild cognitive impairment (memory and thinking problems) due to Alzheimer's disease and early-stage Alzheimer's disease.

Leqembi contains the active substance lecanemab and was 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 and was thereby expected to delay worsening of the disease.

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.

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What were the main reasons for refusing the marketing authorisation?

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. EMA's human medicines committee, the CHMP, considered that the observed effect of Leqembi on delaying cognitive decline does not counterbalance the risk of serious adverse events associated with the medicine.

The most important safety concern with Leqembi is the frequent occurrence of amyloid-related imaging abnormalities (ARIA), a side effect, seen in brain imaging, that involves swelling and potential bleedings in the brain. Although most cases of ARIA in the main study were not serious and did not involve symptoms, some patients had serious events, including large bleeds in the brain which required hospitalisation. The seriousness of this side effect should be considered in the context of the small effect seen with the medicine.

In addition, the CHMP was concerned by the fact that the risk of ARIA is more pronounced in people who have a certain form of the gene for the protein apolipoprotein E called *ApoE4*. The risk is highest in people with 2 copies of the *ApoE4* gene, who are known to be at risk of developing Alzheimer's disease and would therefore be likely to become eligible for treatment with Leqembi.

In reaching its opinion, the CHMP also considered the views of a scientific advisory group on neurology, which included experts such as neurologists and people living with the disease.

Overall, the CHMP considered that the benefits of treatment are not large enough to outweigh the risks associated with Leqembi. Therefore, it recommended refusing marketing authorisation in the EU.

Does this refusal affect patients in clinical trials?

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

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