2024-08-19

To: the Swedish members of Committee for Medical Product for Human Use (CHMP) of the European Medicines Agency (EMA), and Swedish members of the European Parliament

Regarding the decision by the European Medicines Agency to refuse marketing authorization for Leqembi (lecanemab)

Who are we?

We who sign this letter are Swedish physicians and researchers with many years of clinical and research experience in the field of Alzheimer's disease (AD), including physicians responsible for clinical trials and investigators who participated in the clinical studies of lecanemab. We are also involved in patient organizations supporting this exposed and vulnerable patient group.

Why are we writing this?

On July 26, the EMA announced its decision to refuse marketing authorization for lecanemab (Leqembi, Eisai). This drug has previously been approved for clinical use in all countries where assessment has been completed, including the Unites States, Japan, China, Hong Kong, South Korea, Israel and the United Arab Emirates. Indeed, it represents the first clinically meaningful advancement in the disease-modifying treatment of Alzheimer's disease, a severe and fatal disease.

Over 18 months, the Clarity-AD study of lecanemab met all primary and secondary endpoints, which included cognitive test results, cognitive symptoms, impairment in activities of daily living (ADL), quality of life, and caregiver burden. The study demonstrated a 27% slowing of disease progression, in the primary outcome measure—Clinical Dementia Rating-Sum of Boxes (CDR-SB), which assesses the severity of cognitive symptoms. This corresponds to a delay of approximately 5-6 months during the relatively short study period of 18 months. Additionally, lecanemab showed a 37% reduction in the progression of ADL impairment, and significant improvement in quality of life.

Delaying disease progression is crucial for patients, and these effects are significant and meaningful. Moreover, the data indicate that the clinical benefits increase progressively over the study period, consistent with the expected effects of a disease-modifying drug rather than a purely symptomatic treatment. This disease-modifying potential is further supported by the slowing of tau accumulation, a downstream pathology more closely linked to the symptoms of the disease. This was further highlighted by open-label extension data presented at the AAIC conference on July 30. The difference between treated and untreated patients in CDR-SB had increased from 0.45 at 18 months to 0.95 at 36 months compared with historic controls.

These positive treatment effects need to be balanced against the risk of adverse events. Symptomatic amyloid-related imaging abnormalities (ARIA-E) were reported in 2.8% of patients. Most of these events resolved within weeks or months after treatment was discontinued, thus the long-term health effects are likely limited, even in the small number of subjects who experience these events. Further, there are clearly identified risk factors for serious adverse events, including the risk gene *APOE* $\varepsilon 4/\varepsilon 4$ (this gene is only present in 15% of the patient population). This provides the opportunity to restrict treatment to patients where the drug has a favorable risk-benefit profile and carefully define conditions for initiating and follow-up of treatment.

Achieving even greater efficacy and reducing the impact of adverse events will be a key objective in coming years, by optimizing the use of available therapies and through new drug development and investigating combination therapies. For instance, excluding patients with a high tau tangle load would improve outcomes in those treated. Such strategies are increasingly feasible in clinical practice with novel biomarker development. However, these efforts will be severely limited without the ability to use and gain experience with the new therapies in routine care. Sweden and other European countries have industry-independent registry infrastructure in place to prospectively collect data on the long-term safety and effectiveness of novel AD therapies and gain knowledge on their optimal use in routine care. This will allow questions to be answered that cannot be addressed in randomized controlled trials.

What do we want?

We believe it is of great importance that patients with early AD have access to new advances with immunotherapies that have demonstrated clinical benefits. Great caution must be exercised with respect to ARIA events, however the risks of swelling and bleeding in the brain are manageable in clinical practice through adequate inclusion criteria and monitoring, as is now becoming evident in many American clinical centers.

The severe and fatal course of the disease must be considered when assessing the risk-benefit of treatment. In other fatal conditions such as cancer, drugs with major adverse effects have received marketing authorization despite uncertain efficacy. We also urge EMA to not only consider the difference between treatment and placebo groups at the 18-month mark but take into consideration the slowing of disease progression that could have great effects over the more than a decade long symptomatic phase of the disease.

Further, we suggest that in the event of a reconsideration of the decision, the EMA should create clear guidance including recommendations on which patients can be considered for treatment. This approach would mean that the group of patients who respond best to the treatment and have the lowest risk of side effects would have access to the drug in Sweden and the rest of the EU. This would ameliorate the burden on our entire healthcare system and provide the opportunity to collect real-world data. Patients and their physicians will then have the opportunity to weight risks and benefits and make individualized treatment decisions, as is done in the treatment of other serious diseases.

Sincerely,

(in alphabetical order)
Kaj Blennow MD, professor
Nenad Bogdanovic MD, professor
Anne Börjesson-Hanson, MD, PhD
Maria Eriksdotter MD, professor
Oskar Hansson MD, professor
Vesna Jelic MD, associate professor
Michael Jonsson MD, PhD
Linus Jönsson MD, professor
Miia Kivipelto MD, professor
Katarina Nägga MD, professor
Sebastian Palmqvist MD, associate professor
Michael Schöll, professor
Anders Wimo MD, professor emeritus
Bengt Winblad MD, professor emeritus
Henrik Zetterberg MD, professor
Henrik Östlund, MD