

Lecanemab: The Price of a Breakthrough

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On 6 January 2023, the amyloid beta-targeting antibody lecanemab was approved by the US Food and Drug Administration for the treatment of mild cognitive impairment due to Alzheimer's disease (AD) and mild AD dementia via its Accelerated Approval pathway. However, two important questions need to be highlighted: What is the appropriate patient population to receive treatment? How much should healthcare systems be prepared to pay for the drug? The healthcare infrastructure is not prepared for the expected huge demands for diagnostics and eventual treatment, especially given the suggested list price and a potentially large population of people with mild cognitive impairment due to AD and mild AD dementia. A lower price point would allow wider access to the treatment and reduce disparities in health equity.

Keywords

Alzheimer's disease, costs, disease-modifying treatment, drug price, lecanemab

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After so many failures, we finally got the positive signal that we have been waiting for: a disease-modifying treatment that might work for Alzheimer's disease (AD). On 6 January 2023, lecanemab, a humanized immunoglobulin G1 version of a mouse monoclonal antibody that selectively binds to large, soluble amyloid-beta (A β) protofibrils, was approved by the US Food and Drug Administration (FDA) via their Accelerated Approval pathway, which is reserved for therapies for diseases with few treatments.¹ Following the Breakthrough Therapy designation from the FDA in 2021,² Lecanemab showed positive results in early-stage AD, a lesser decline in cognition and function compared with placebo after 18 months of treatment. These results were presented at the Clinical Trials on Alzheimer's Disease conference in San Francisco, CA, US, on 29 November 2022³ and published in the *New England Journal of Medicine* on 5 January 2023.⁴ As the second disease-modifying agent for AD to be approved after aducanumab,⁵ this news incites hope and provides support for the amyloid hypothesis of AD molecular pathogenesis.

Despite this encouraging development, there are still many concerns. Lecanemab does not cure AD but seems to reduce the rate of disease progression by approximately 27%.⁴ Moreover, will these statistically significant results be maintained and prove to be clinically meaningful in the long run? How will potential adverse events, such as amyloid-related imaging abnormalities, be managed, and what will be the risk of clinically severe adverse events in unselected patient populations?

Besides these concerns, we wish to highlight two other important questions:

1. What is the appropriate patient population to receive treatment?
2. How much should healthcare systems be prepared to pay for the drug?

These two questions are closely related.

For drugs used in large patient populations, the cost of the treatment must be proven to be manageable and at a level commensurate to the value of the health benefits delivered. However, among the drugs used for small and well-defined patient populations, there have recently been examples of products that have been priced and reimbursed at much higher levels, even when considering the often substantial clinical benefits of such orphan drugs. At the launch of aducanumab, there was an attempt to combine a large potential target population with a very high price.⁵ Similar to aducanumab, the FDA-approved indication for lecanemab is the treatment of AD in patients with mild cognitive impairment (MCI) or mild dementia. The number of people living with MCI and mild AD dementia is enormous globally, standing in the tens of millions.⁶ For example, in Sweden, a conservative estimate is that about 100,000 persons out of a population of about 2 million persons aged 65 and above may fit these criteria and, therefore, be potentially eligible for treatment.⁷

Linked to the discussions of the target population is the capacity of the diagnostic infrastructure to recognize MCI due to AD and mild AD dementia. There may be huge demands from the general population for diagnosis and eventual treatment. The introduction of lecanemab will thus increase the costs in the healthcare system also for patients that will never be treated with the drug. These diagnostic costs must be included when estimating the cost-effectiveness of the treatment.

Blood-based biomarkers combined with cognitive testing targeted to detect slight symptoms of cognitive impairment may serve as a "filter" in primary care to identify people at risk of having early-stage AD. However, we don't yet know how this diagnostic process would perform on a large scale, and the capacity in primary care is limited in most countries. At the next diagnostic level, specialists at memory clinics (or equivalent) are being subjected to even greater capacity challenges.

Eisai Co., Ltd. (Tokyo, Japan), has reportedly set the list price for lecanemab to US\$26,500 per year of therapy.⁸ If this price is applied to the entire eligible patient population in Sweden, for example, the aggregated annual drug cost would be US\$2.65 billion, compared with the total aggregate cost for prescription pharmaceuticals in Sweden of US\$3.3 billion in 2021.⁹ Therefore, one single drug with significant but modest effects would, if used within its full licensed indication, consume about 80% of the total drug spending. Since people will be treated for many years (no stopping rules are at hand yet; on-going follow-up studies may provide some guidance in this regard), costs will aggregate over time.

This scenario is clearly unrealistic – the aforementioned barriers to diagnosis and treatment will necessarily limit the number of treated patients. A high acquisition cost will also require healthcare systems to reduce the number of treated patients even further or even refuse reimbursement altogether. There is currently very limited evidence to support which patient groups should be prioritized for treatment; therefore, such decisions may primarily be driven by the availability of resources and ability to pay, thus magnifying disparities and health inequality between and within countries.

A lower price point would conversely allow wider access to the treatment, reducing such disparities. It would also create more opportunities for collecting real-world data on the performance of lecanemab as used in routine care, which may provide valuable guidance on maximizing clinical benefits while limiting the risk of adverse events.

To stop the spread of AD, novel therapies beyond lecanemab will be needed. Appropriate incentives for continued investment in pharmaceutical innovation and development are therefore essential. Overpayment for modest innovations may lead to the waste of resources for future AD research, giving incentives to focus on "half-way technologies" rather than projects that may lead to real progress towards a cure for the disease.

A failure of the pricing and reimbursement mechanisms to establish access for patients to new, approved treatments at a price that corresponds better to the demonstrated clinical benefits of the therapy may have repercussions for future research and development investment in this field. It is, therefore, essential that pricing discussions are guided by the best available data from trials, epidemiological studies and health economic modelling. Eisai has shared results from their calculation of the societal value of lecanemab, based on clinical data that "could potentially translate into impactful outcomes".⁸ The considerable uncertainty around long-term treatment benefits should have consequences for the value-based price, and independent estimates are needed.

It is indeed hopeful that disease-modifying treatment work for AD. However, price matters. Our hope is that pricing and reimbursement discussions will result in a reasonable price for this groundbreaking discovery, considering the uncertainty of the long-term health effects of treatment.

So, similarly to what a great statesman once said, this is not the end (of the AD nightmare), it is not even the beginning of the end, but it might be the end of the beginning. □

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