US FDA defends approval of Alzheimer's disease drug

Accelerated approval for aducanumab has prompted resignations and condemnation of the agency's decision. Susan Jaffe reports from Washington, DC.

For the **FDA's scientific review documents for aducanumab** see https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178_Orig1s000TOC.cfm

An avalanche of criticism has forced the US Food and Drug Administration (FDA) to defend its decision to grant accelerated approval for the first new Alzheimer's disease treatment in two decades. Three physicians who were members of an FDA advisory committee that recommended against approving the drug, Biogen's aducanumab (also known as Aduhelm), resigned in protest. Then came duelling opinion articles from the FDA and a former committee member, and media appearances by supporters and detractors, capped last week by the FDA's release of internal scientific review documents explaining its decision. The disclosures have not satisfied two congressional committees planning to investigate why the FDA approved the drug despite questions about its clinical benefits. "I don't think I've ever seen this kind of a reaction", said Ronald Petersen, director of the Mayo Clinic's Alzheimer's Disease Research Center (Rochester, MN) and professor of neurology, who has consulted for Biogen but was not involved the aducanumab studies.

Among the documents is a memorandum that describes an April, 2021, meeting of FDA officials. All but one agreed that aducanumab qualified for special accelerated approval. Sylva Collins, director of the Office of Biostatistics, dissented, "stating her belief that there is insufficient evidence to support accelerated approval or any other type of approval", according to the memorandum.

More than 6·2 million Americans have Alzheimer's disease, and this number is expected to double by 2060.

Instead of full approval, the FDA opted for accelerated, or conditional, approval for aducanumab, which does not require Biogen to show that its drug could reduce or slow the progressive loss of cognitive function caused by the disease. In lieu of evidence of clinical improvement, the agency based its decision on the drug's effect on a surrogate biomarker—its ability to reduce amyloid β plaque in the brain. However, there is not a clear consensus on how these substances contribute to cognitive decline.

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Accelerated approval was created under a 2012 federal law to increase access to needed drugs for diseases that had little or no treatment option even when such medications were not proven to improve patients' conditions.

The FDA also required Biogen to conduct a post-marketing study to determine whether the drug improves memory or slows the disease's progress. Patients receiving aducanumab must also receive periodic brain scans to detect side-effects including brain swelling or bleeding. "It will be a very long time before we ever figure out whether or not this drug really works because the FDA gave the company 9 years to complete its post-approval confirmatory trial", said Aaron Kesselheim, professor of medicine at Brigham and Women's Hospital and Harvard Medical School (Boston, MA), who resigned from the advisory panel in protest. "And that is unfortunate because during that time, it will be given to a lot of people, and those people will be put at risk of the side-effects of the drug, and it will cost the health-care system a lot of money."

Biogen intends to charge US$56 000 annually for the drug. That price excludes the scans, which can range from about $4000 to $7000 each, to detect adverse reactions, costs to detect amyloid in patients' brains before receiving the drug, and costs for intravenous administration. Government health insurance programmes as well as private insurers have not yet indicated whether they will cover all the costs for all eligible patients. Biogen's chief executive officer, Michel Vounatsos, defended aducanumab's price tag, explaining in an open letter on the company's website that it "reflects the overall value this treatment brings to patients, caregivers, and society—and one that will enable continuous innovation."

Several experts cautioned that the drug is not appropriate for all patients with Alzheimer's disease. They said prescribers should follow the inclusion criteria used to select participants in the drug's clinical trials: patients with mild symptoms and evidence of amyloid plaques in the brain who can participate in the decision-making process. "The clinical diagnosis of Alzheimer's disease is not sufficient, in my estimation, for prescribing the drug because it shouldn't work in somebody who doesn't have amyloid", said Jeffrey Kaye, professor of neurology at the Oregon Health and Science University's School of Medicine and director of its Layton Aging and Alzheimer's Disease Center (Portland, OR).

Some researchers welcomed the FDA's decision because it makes it easier for other pharmaceutical developers to seek accelerated approval for Alzheimer's disease drugs. Researchers will not have to "come up with a drug to treat the disease symptoms and improve cognition", said Rudolph Tanzi, professor of neurology at Harvard Medical School and director of Massachusetts General Hospital's Genetics and Aging Research Unit (Boston, MA). The decision "opens the floodgates", he said.

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