

# ***New Federal Decisions Make Alzheimer’s Drug Leqembi Widely Accessible***

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The F.D.A. gave full approval to the drug but added a black-box warning about safety risks. Medicare said it would cover most of the high cost.

The Food and Drug Administration on Thursday [gave full approval to the Alzheimer’s drug Leqembi](#), and Medicare said it would cover much of its high cost, laying the foundation for widespread use of a medication that can modestly slow cognitive decline in the early stages of the disease but also carries significant safety risks.

The F.D.A.’s decision marks the first time in two decades that a drug for Alzheimer’s has received full approval, meaning that the agency concluded there is solid evidence of potential benefit. But the agency also added a so-called black-box warning — the most urgent level — on [the drug’s label](#), stating that in rare cases the drug can cause “serious and life-threatening events” and that there have been cases of brain bleeding, “some of which have been fatal.”

Leqembi cannot repair cognitive damage, reverse the course of the disease or stop it from getting worse. But data from a large clinical trial suggests that the drug — administered every two weeks as an intravenous infusion — may slow decline by about five months over about 18 months for people with mild symptoms.

Still, some Alzheimer’s experts have said it is [unclear from the medical evidence](#) whether Leqembi’s ability to delay erosion of memory and cognition would be enough to be noticeable or meaningful for patients and their families. And while most cases of brain swelling and bleeding have been mild or moderate and have resolved, there have been some serious cases.

“The risks are very vivid,” said Dr. Jason Karlawish, a co-director of the University of Pennsylvania’s Penn Memory Center, who said he will prescribe Leqembi after carefully evaluating patients and explaining the potential pros and cons. “Within the first few months, you may have small bleeds or swelling in your brain, which may or may not be symptomatic and if not detected in time can cause disability.” “In contrast,” Dr. Karlawish continued, “the benefits of slowing are subtle. You’re not going to experience the perception of changes in your cognition or function in the same amount of time.”

Though Medicare will cover 80 percent of Leqembi’s \$26,500 cost, patients could still shoulder thousands of dollars in co-payments. Eisai, a Japanese pharmaceutical company, led the development and testing of Leqembi (pronounced le-KEM-bee). Eisai is partnering and splitting profits with the American company Biogen, the maker of the controversial Alzheimer’s drug Aduhelm, for its commercialization and marketing.

The F.D.A.'s approval of Aduhelm was severely criticized because the evidence of potential benefit was inconclusive, with one trial showing modest slowing of decline but another showing no slowing. Before that approval, a committee of independent advisers and an F.D.A. council of senior officials said [there was not enough evidence that it worked](#). Many medical centers [declined to prescribe](#) Aduhelm, and Medicare has covered it only for clinical trial participants, [sharply restricting its availability](#). Evidence supporting Leqembi is much clearer, Alzheimer's experts said.

Leqembi will be available for people with mild dementia or a pre-Alzheimer's condition called mild cognitive impairment. The F.D.A. label instructs doctors not to treat patients without testing to confirm they have an accumulation of the protein amyloid, a hallmark of Alzheimer's that Leqembi attacks.

About 1.5 million people in the United States are estimated to be in the beginning phases of Alzheimer's. Many more — about five million — have progressed too far to be eligible for Leqembi. Alex Scott, Eisai's executive vice president of integrity, said the company recommends patients stop using Leqembi once they develop moderate Alzheimer's disease.

Alzheimer's experts said they would inform some patients that they had greater risk for brain swelling and bleeding — including those taking blood thinners, those with more than four microscopic bleeds in the brain and those with an Alzheimer's-linked gene mutation called APOE4.

The risk to people with two copies of the APOE4 mutation — about 15 percent of people with Alzheimer's — is so high that the F.D.A.'s black-box warning recommends that all patients be genetically tested to assess their safety risk and spells out that those with two APOE4 copies are more vulnerable to developing “symptomatic, serious and severe” brain bleeding or swelling.

The black-box warning will apply to all drugs that, like Leqembi, are monoclonal antibodies that attack amyloid. Leqembi is the first to get full approval, but others are in various stages of development.

The warning does not mention patients who are taking blood thinners, but Leqembi's label says that “additional caution should be exercised” when considering whether to give blood thinners to Leqembi patients.

The F.D.A. greenlighted Aduhelm under a program called “accelerated approval,” which can be given to drugs with uncertain benefit under specific criteria, including that the company conduct another clinical trial. Leqembi received accelerated approval in January, but that status meant Medicare would only cover the drug in limited circumstances.

The F.D.A. decision granting full approval to Leqembi means that Medicare will cover it for eligible patients. Still, some patients will be unable to afford the 20 percent Medicare does not cover, possibly about \$6,600 a year. Including costs of medical visits

and required regular brain scans, some of which will receive Medicare reimbursement, the treatment could run to about [\\$90,000 a year](#), some experts estimate.

[A recent study](#) estimated that covering the drug and necessary services for about 85,000 patients would cost Medicare \$2 billion a year and would climb to \$5.1 billion if the number of patients reached about 216,000. That could lead to an increase in premiums for all Medicare beneficiaries, not just those receiving Leqembi, the study said.

In interviews, Ivan Cheung, the chairman and chief executive of Eisai's United States operations, estimated that in the first three years, about 100,000 patients would be receiving the drug.

The Medicare agency is adding a requirement [that doctors prescribing Leqembi submit medical information](#) about each patient before and while they are being treated with the drug. The information will be kept in patient registries and evaluated to learn more about Leqembi's benefits or harms, the agency said. "With F.D.A.'s decision, C.M.S. will cover this medication broadly while continuing to gather data that will help us understand how the drug works," the administrator of the Centers for Medicare and Medicaid Services, Chiquita Brooks-LaSure, said in a statement.

Some advocacy groups, like the Alzheimer's Association, have [criticized the registry requirement](#), calling it an unnecessary barrier to access. But medical experts say registry programs are common and easy to comply with. Their concern is that the registry won't be comparing Leqembi patients with others, so it won't be able to say if Leqembi slows cognitive decline.

The F.D.A.'s approval on Thursday was based on a large trial indicating that patients receiving Leqembi declined 27 percent more slowly over 18 months than patients receiving a placebo. The difference between those receiving drug and placebo was small — less than half a point, on an 18-point cognitive scale that assesses functions like memory and problem-solving. Some Alzheimer's experts say that for slowing of decline to be clinically meaningful, or noticeable to patients and families, the difference between the groups must be at least one point.

Leqembi patients also declined more slowly on three secondary measures of cognition and daily function, and data on biological markers was generally stronger for Leqembi than for the placebo. All these measures moving in the same direction strengthens the idea that the drug can benefit patients, experts say.

Still, a report on the data, [published](#) in The New England Journal of Medicine and co-written by scientists from Eisai, concluded that "longer trials are warranted to determine the efficacy and safety." Concerns about safety have been stoked by reports of [deaths](#) of three clinical trial participants who experienced brain swelling and brain bleeding, two of whom were being treated with blood thinners. Eisai has said it is unclear if Leqembi contributed to their deaths because the patients had complex medical issues.

“You’ve got small benefits and a certain risk for serious adverse events, and that has to be balanced,” said Dr. Lon Schneider, director of the California Alzheimer’s Disease Center at the University of Southern California, who said he will prescribe Leqembi to carefully evaluated patients. “If its efficacy were greater, we would not be talking about adverse events as much because we would see a clear benefit,” he said, adding, “I think many people will see this and say it’s not worth the effort, it’s not worth twice-a-month infusions.”

Dr. Karlawish said the decisions facing patients and families will be complicated. Because eligible patients have only mild symptoms of cognitive decline, some might opt to take any medication that might prolong that relatively functional stage, while others might only consider the risks of the drug worthwhile if they were much more impaired. Dr. Karlawish said one recent patient declined to get evaluated for potential treatment, indicating that “I want more benefits, I don’t see the value.” But, he said, “I have other patients, though, who would say, you mean you can give me a drug that could slow the disease?”

In the trial, nearly 13 percent of patients receiving Leqembi experienced brain swelling, which was mostly mild or moderate, while less than 2 percent of patients receiving the placebo experienced such swelling. Most brain swelling did not cause any symptoms, generally emerged soon after use began and resolved within a few months. About 17 percent of Leqembi patients experienced brain bleeding, compared with 9 percent of patients receiving a placebo. The most common symptom from brain bleeds was dizziness.

Overall, the results suggest the risk of brain bleeding and swelling was significantly lower than for patients in [trials of Aduhelm](#). Dr. Jerry Avorn, a professor of medicine at Harvard Medical School who studies medication regulation and use, said doctors will feel pressure to prescribe Leqembi from patients, families, and advocacy organizations. Medical institutions will also have an “enormous financial incentive” because of the Medicare reimbursement that “they could then spend on social workers and all the other things that Medicare will not reimburse,” he said, adding “any economically self-respecting memory center is going to see this as an economic windfall.”



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