FDA gives full approval to first drug to clearly, but modestly, slow Alzheimer's

Leqembi, administered intravenously every other week, will get a "boxed warning" because it can cause brain bleeding and swelling

The Food and Drug Administration on Thursday gave full approval, for the first time, to a **drug that modestly slows Alzheimer's disease** — a development that offers a degree of hope for treating the memory-robbing disease but also raises difficult questions about safety, effectiveness and cost.

The agency had previously granted the drug, called leqembi, accelerated approval based on its ability to **reduce amyloid clumps in the brain, a hallmark of Alzheimer's**. Thursday's action was based on later-stage data that showed the treatment **slowed cognitive and functional decline by 27 percent over 18 months** compared with placebo. That represented a five-month slowdown in progression, experts said.

"*Today's action is the first verification that a drug targeting the underlying disease process of Alzheimer's disease has shown clinical benefit in this devastating disease,*" said Teresa Buracchio, acting director of the Office of Neuroscience in the FDA's Center for Drug Evaluation and Research. "*This confirmatory study verified that it is a safe and effective treatment for patients with Alzheimer's disease*."

The FDA action means **the drug will be available to a broader swath of people, Medicare said** Thursday. The health program for older Americans declined to pay for the drug outside of clinical trials after it received accelerated approval. **But Medicare said the treatment would be covered once it received full FDA approval** — as long as prescribers participate in registries that collect evidence about how Leqembi works in the real world.

Leqembi, which is given intravenously every other week, **is for early-stage patients with mild cognitive impairment or early dementia caused by Alzheimer's, and a confirmed buildup of amyloid in their brains**.

The FDA said the drug's label will include a "boxed warning" highlighting safety issues. That warning, sometimes called a "black box," says that **Leqembi, and other members of a new class of anti-amyloid drugs, can cause brain swelling and bleeding.** The side effect, called ARIA **— amyloid-related imaging abnormalities** — usually is asymptomatic and managed safely. But life-threatening incidents can occur in rare cases, the FDA said. Three patient deaths in an extended portion of Leqembi's main trial were thought to be linked to the drug. **About 21 percent of trial participants who received the drug experienced ARIA, but only a small percentage had symptoms**. About 9 percent of those who received the placebo had the side effect.

The boxed warning also says that patients with two copies of a genetic variant that increases the risk of developing Alzheimer's — called APOE4 — appear to be at considerably higher risk of complications from Leqembi. The FDA recommended, but did not require, that ***genetic testing occur before a patient receives the drug.***

The FDA in other instructions **urges physicians to use caution in prescribing Leqembi to people on blood thinners.** Some clinics have said they don't plan to give the drug to people on blood thinners because of concerns about possible bleeding in the brain.

Leqembi, from the pharmaceutical company Eisai in Tokyo and Biogen in Cambridge, Mass., is a monoclonal antibody, or lab-made protein, that targets amyloid beta in the brain. It is not a cure and does not restore memories ravaged by the fatal neurodegenerative disease. But many neurologists say having a drug that slows Alzheimer's, even modestly, is a milestone after years of failed drug trials.

Nevertheless, the drug's side effects, and its **$26,500-a-year price tag,** have generated controversy about the medication, **also called lecanemab**. Some doctors are skeptical, saying the drug is not effective enough. Others doubt amyloid is the root cause of Alzheimer's. Jerry Avorn, professor of medicine at Harvard Medical School, worries patients ***will wrongly expect the medication to improve their memory and thinking skills***. "*That's untrue*," he said. "***It will just make Grandma forget a tiny bit less."*** And he noted that patients who get the drug will have to undergo multiple brain scans and **make frequent trips to infusion centers**, which could be a burden.

Some skeptics have said patients might not notice the effects of the drug. In an editorial last December, after the results from the pivotal trial were released, the British medical journal Lancet said the drug's impact might "not be clinically meaningful" and urged physicians to highlight reducing risk factors for dementia such as hypertension, smoking, diabetes and obesity. But Ivan Cheung, chairman and CEO of Eisai in the United States, said in an interview Thursday the data clearly shows the drug is "clinically meaningful" for patients and also provides "societal value" to caregivers and families. He said the approval Thursday was a "triumph" for patients, families and those who treat Alzheimer's after decades of hard work and dashed hopes.

Keith Vossel, director of the Alzheimer's center at UCLA, said he was excited about Leqembi, calling it "a breakthrough scientifically." But he added that **dementia experts would have to carefully explain the medication's benefits and risks.** Usually, initial visits with patients last about an hour, but "just a discussion on Leqembi could take 30 minutes because it requires a lengthy discussion of how the drug works, and what that means," he said. Vossel said the clinic will have an "amyloid infusion core" of experts to review patients who meet the initial screening requirements to **ensure the drug is appropriate.** He said the group would operate like a "tumor board" does for cancer cases.

Two years ago, the FDA granted accelerated approval to another antibody drug called **Aduhelm.** Some of the trial data indicated that medication slowed Alzheimer's, but the information was so confusing and contradictory that Aduhelm failed in the marketplace and never received traditional approval.

More than 6.5 million Americans are living with Alzheimer's — and that number does not include many people with mild cognitive impairment who often are not diagnosed. Pamela Spicer, therapy area director at Citeline, a company that tracks global drug development, predicted **the initial demand for Leqembi would be subdued**. "The rollout is not going to be immediate," she said. Even at academic medical centers, where the drug is likely to be offered, it might take months for doctors to establish safety protocols and learn how to secure Medicare coverage for patients.

The Medicare requirement that patients and providers enroll in registries has been harshly criticized by some advocacy groups, including the Alzheimer's Association. They say some doctors might not want to take part in a registry, curbing access for patients. In the past, such registries have mostly been used for complex medical devices, not drugs. But many physicians say gathering data about how Leqembi affects patients could prove helpful in answering questions and is not a significant burden.

In a statement Thursday, Chiquita Brooks-LaSure, administrator of Centers for Medicare and Medicaid Services, said, "*With FDA's decision, CMS will cover this medication broadly while continuing to gather data that will help us understand how the drug works*." **Even with Medicare coverage, patients could face thousands of dollars in drug bills; typically patients are responsible for 20 percent of the cost of infused drugs**.
And it is not clear whether other tests, including genetic ones, will be covered. Most patients who are likely to get the drug are expected to be in Medicare because of their age or, if they are younger than 65, because they are receiving Social Security disability benefits.
The Department of Veterans Affairs already covers the drug, although not for people who have two copies of the APOE4 gene. Private insurers often follow Medicare's lead.

John Driscoll, 80, who lives in Manhattan Beach, Calif., has been getting Leqembi for three years as part of the trial, called Clarity AD. At first, he received infusions but now injects himself in the thigh as part of a study to test self-administration, a formulation not yet approved by the FDA.

Driscoll, who is being treated at UCLA, said he believes the drug, along with the support of a large and loving family, is slowing his decline, though he does not know by how much. “My memory loss now is not overwhelming,” he said.

But he acknowledges the drug will not keep him from getting worse. “I’m choosing not to pout or cry about it,” he said. “I just keep going forward.”

Laurie Scherrer of Albertville, Ala., who was diagnosed with early-onset Alzheimer’s a decade ago at age 55, said she had a bad experience with Aricept, which treats symptoms such as confusion, and is not interested in Leqembi.

“I have found that having a purpose and a positive attitude and mind-set, and getting exercise and fresh air, has worked better than any drug could,” said Scherrer, who is on the board of an organization called Dementia Action Alliance that runs support groups and activities for people with dementia. “A drug does not get you up out of the recliner.”

Another anti-amyloid drug, by Eli Lilly, is on the horizon. The company is expected to release details of the data from its main clinical trial for donanemab this month, and may get FDA approval at the end of the year or early next year.

The arrival of two anti-amyloid drugs could mean billions of dollars in additional Medicare spending, analysts say, but the exact cost depends on how many patients receive them, which is not known.

Eisai has forecast that 100,000 people will be eligible to receive Leqembi or a similar drug after three years, but many analysts say the estimate is too low.

Amyloid is thought to be one factor — although not the only one — that contributes to Alzheimer’s. Clinical trials also are testing drugs that target inflammation and tau tangles, another characteristic signature of Alzheimer’s.

To be eligible for Leqembi, patients will need evidence they have a buildup of amyloid in their brains — as determined by lumbar punctures, also known as spinal taps, or by costly PET scans generally not covered by Medicare.

Joanne Pike, president and CEO of the Alzheimer’s Association, which has been pressing Medicare to provide unfettered coverage of Leqembi, said people should not underestimate the value of even a few months of slower decline.

“This gives people more months of recognizing their spouse, children and grandchildren,” Pike said in a statement. “This also means more time for a person to drive safely, accurately and promptly take care of family finances, and participate fully in hobbies and interests.”

Avorn, of Harvard, views it differently and plans a “demarketing” campaign to highlight the drawbacks of Leqembi. He hopes to discourage primary-care doctors from referring patients to memory clinics to get Leqembi.

“If this were an improvement, I would say, ‘Hooray, let’s do it,’” Avorn added. “But once people see it is a modest slowing of decline, people will weigh it more carefully.”

University of Kansas neurologist Jeffrey M. Burns acknowledged that doctors need more information about how the drug works. “It may be an incremental change or a huge step forward,” he said. “But it is a whole new era. Finding patients who might respond is a whole new way of going after the disease.”