Inside the tactical tug of war over the controversial Alzheimer's drug

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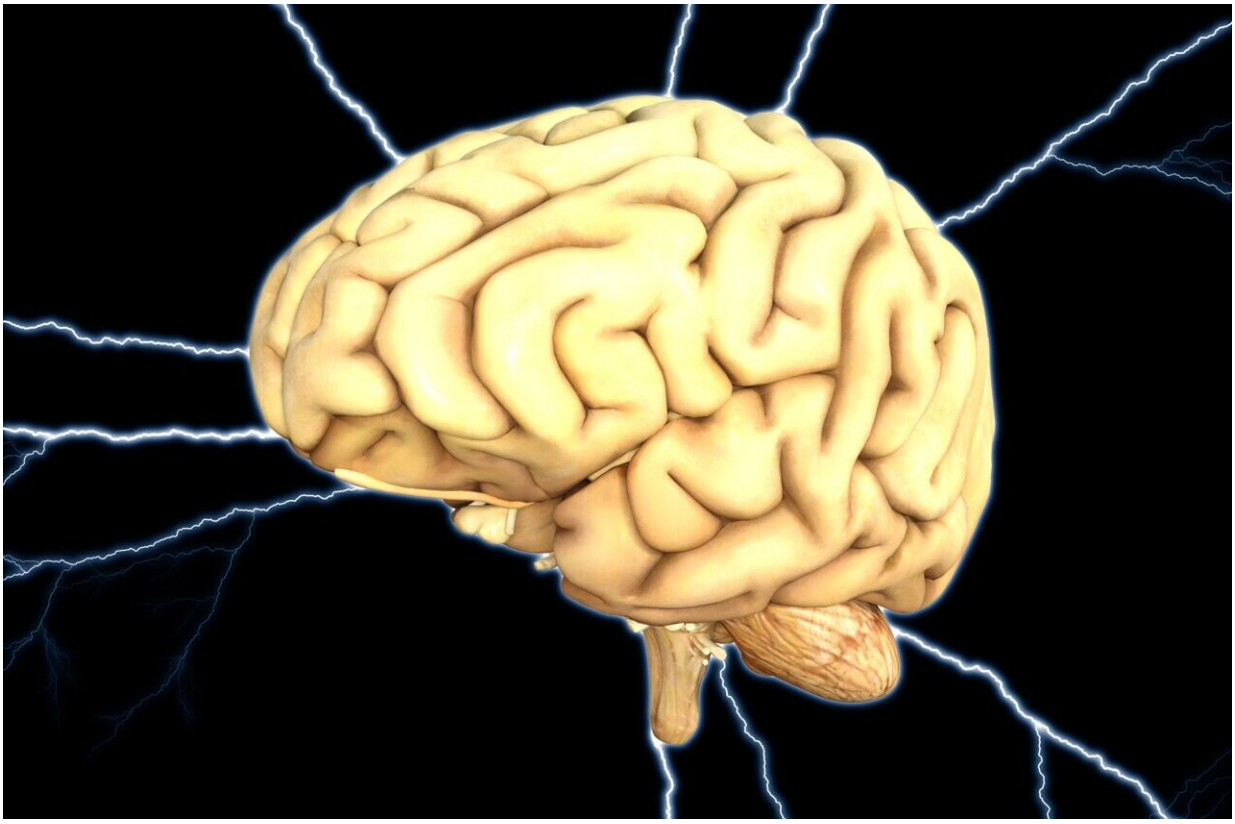

Credit: Pixabay/Pete Linforth.

The drug industry, patient advocates and congressional Republicans have all attacked federal officials' decision to decline routine Medicare coverage for a controversial Alzheimer's drug. They've gone as far as to

accuse them of tacit racism, ageism and discrimination against the disabled—and hinted at a lawsuit—over the decision to pay only for patients taking the drug in a clinical trial.

The drug, Aduhelm, with a listed price tag of $28,200 a year, has had few takers in the medical world. Brain doctors are leery of administering the intravenous drug because it appears dangerous and largely ineffective. Many of the nation's most prestigious hospitals—such as the Cleveland Clinic, Johns Hopkins Hospital and Massachusetts General in Boston—have declined to offer it to patients.

While groups representing the pharmaceutical industry and patients press to undo Medicare's decision, industry critics applaud the Centers for Medicare & Medicaid Services for throwing obstacles in the way of a drug they think the FDA should never have approved in the first place.

For the industry, the campaign has a broader existential target: to prevent CMS from using its payment decisions to keep FDA-approved drugs off the market. In recent years, FDA programs to speed approval of new drugs have led to a rash of entries with often minimal scientifically sound evidence to prove they work, critics say.

The FDA's own expert panel recommended against approving Aduhelm for that reason. Last June, the agency approved it anyway.

CMS then announced Medicare would pay only when the drug was used in further clinical trials to assess its true benefit. That Jan. 11 announcement has drawn more than 9,000 comments to the agency's website—a tsunami compared with most approval decisions. The remarks are roughly divided among pros and cons, and many appear to be organized by groups on the pro side of the debate (such as the Alzheimer's Association) or those opposed (such as the nonprofit More Perfect Union). The agency could change or even reverse its decision,

though experts believe the latter is unlikely.

"If the FDA were doing its job, CMS wouldn't have had to step in. But good for the CMS, they are helping to protect the public from drugs whose harms outweigh benefits," said Dr. Adriane Fugh-Berman, a Georgetown University professor of pharmacology who directs PharmedOut, a group that publicizes what it sees as poor industry practices.

Aduhelm is the first FDA approval for a class of laboratory-made antibodies designed to clear away so-called amyloid plaques, which gradually accumulate in the brains of people with Alzheimer's disease.

In clinical trials, Aduhelm did well dissolving the plaques, but its impact on the functioning of patients in earlier stages of Alzheimer's was so meager that an expert panel voted 10-0 (an 11th panelist was uncertain) in November 2020 to advise FDA to reject it. The science is unclear about whether the presence of such plaques—a so-called surrogate marker—correlates with the mental functioning of patients.

As such, the FDA gave "provisional approval" to Biogen, the maker of Aduhelm, allowing it nine years to provide evidence that the drug slows the progression of Alzheimer's. In that period, Biogen would make far more money than if the application had been rejected. Even under the CMS decision, it would reap Medicare payments from whatever is used in clinical trials, which would need to include thousands of participants to assess the drug's performance.

Drug companies and pharma investors have responded to CMS' ruling with special alarm because they have spent decades improving their relationships with the FDA, only to have CMS seemingly pull the rug out by exerting its own power over an expensive drug.

"The drug companies are worried that this could be a precedent for other drugs. And it should be," Fugh-Berman said. "This isn't just about money; it's about protecting the public."

This "accelerated approval" employed for Aduhelm got its start in 1992 and is aimed at moving promising new classes of drugs to the public faster. Companies whose drugs go through the process—more than 250 drugs or vaccines have been approved so far—are supposed to quickly gather evidence that the products likely improve health once they're on the market. But such follow-up studies often lag or are never performed. For example, the makers of the Duchenne muscular dystrophy drug eteplirsen, approved in 2016, didn't start recruiting patients into a post-marketing trial until 2020 and don't expect results until 2026.

Biogen originally said it would get confirmatory results for Aduhelm within seven years of approval. In response to the Medicare decision, it promised to trim that to four years. The company also hinted that it might sue the agency, calling its decision "arbitrary and capricious."

In the meantime, patients eager to get access to the drug are furious about the coverage decision. Jim Taylor, a New Yorker whose wife, Geri, says she improved on Aduhelm during a clinical trial, said Medicare had made an "unconscionable decision" that puts Alzheimer's patients "on a dark roller coaster."

Many patients' groups are organized or at least funded and fueled by drugmakers, providing sympathetic stories that buttress a manufacturer's commercial interests. Advocacy groups also receive large donations from the makers of certain drugs. A 2020 report by UsAgainstAlzheimer's shows at least $900,000 in donations from monoclonal antibody producers. The Alzheimer's Association's top corporate donors—Biogen, Lilly, Eisai and Genentech—all have monoclonal antibody candidates and have provided the group $1.6

million in fiscal year 2021.

These donations are a tiny part of the group's funding, its policy director, Robert Egge, told KHN, and any alignment of its position with industry is "coincidental, because of what we and our constituents believe is right."

The Taylors appeared at an online news event with activists from UsAgainstAlzheimer's and the National Minority Quality Forum, a group focused on health inequities, who argued that the decision discriminated against Black and Hispanic patients, who are more likely to suffer from Alzheimer's and less likely to join clinical trials. In fact, CMS demanded that evidence for Aduhelm be collected more extensively from minority patients. Biogen's two major trials of the drug included only 19 Black patients out of a total of 3,285.

Groups representing people with Down syndrome wrote more than 1,000 letters to CMS because its decision requires that confirmatory trials exclude people who have additional neurological conditions. Rep. Cathy McMorris Rodgers, a top drug industry cash recipient and the leading Republican on the House Energy and Commerce Committee with significant sway over pharma issues, said at a hearing last week that it was "extremely concerning and unacceptable" that Down syndrome patients would be ineligible.

But neither Biogen nor any other drug company has recruited Down syndrome patients for a major trial of a monoclonal antibody treatment. AC Immune, a Swiss company, conducted a safety study last year on 16 people with Down syndrome.

It's not surprising that groups representing those suffering from Alzheimer's placed high hopes on the monoclonal antibody drugs, which have seemed like a ray in the darkness for the estimated 2 million

Americans with early Alzheimer's symptoms.

When asked why his group is so gung-ho about a product in which the medical profession shows such little confidence, Egge said the drug seems to have some benefits and that its risks—especially to patients who lack other means to slow a miserable, deadly disease—may be exaggerated. He acknowledged that 40% of patients in the biggest Aduhelm trial experienced brain swelling or bleeding, but Biogen's research showed these resolved with no apparent harm in most cases.

That said, the sluggish purchases of the drug—which earned a modest $1 million in the last quarter of 2021—signal the market is responding to its deficiencies.

In response to the lackluster response, Biogen halved its initial $56,000 price to $28,500. If CMS had granted full approval, that would have been followed by "marketing, marketing, marketing," said Dr. Joseph Ross, a public health professor at Yale University. Hospitals that wanted to attract patient business for a lucrative infusion—patients receiving the drug also require brain scans and other tests and monitoring—could advertise their willingness to give Aduhelm.

CMS' decision came under a policy called coverage with evidence development. Though the program began in 2005, Aduhelm is by far the most important product CMS has declined to reimburse without further study.

The agency's decision "is a little inelegant" because it puts the brakes on an FDA approval, said former CMS chief medical officer Dr. Sean Tunis, now a consultant and senior fellow at Tufts Medical Center, but "it seems completely justifiable since the evidence of benefit is pretty weak and the evidence of harm is pretty strong."

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