Scientific Coalition Letter on Aduhelm to HHS Inspector General

July 7, 2021

Christi Grimm, Acting Inspector General
U.S. Department of Health and Human Services Washington, DC 20201

Dear Ms. Grimm:

As organizations working to promote and protect science for the public good, we are writing to express our concern about the lack of scientific evidence to support the FDA's recent accelerated approval of Biogen's Aduhelm (aducanumab) as a drug intended to slow cognitive damage caused by Alzheimer's disease. Everyone agrees that there is an urgent need for a safe and effective treatment for Alzheimer's disease, and approval of such a treatment would be cause for rejoicing. However, because persuasive evidence of Aduhelm's effectiveness is lacking, and the known risks are substantial, the Food and Drug Administration (FDA) approval instead sets a dangerous precedent and raises concerns about scientific integrity. Our recommendations for next steps are included below.

At the FDA's public Advisory Committee meeting in November, Biogen provided data from two randomized double blind controlled trials of cognitive outcomes: One study showed that the placebo group had a slightly (but not statistically significant) better score on memory, and the other study showed the drug might slightly benefit memory after 78 weeks, but with a difference that experts concluded was "not clinically meaningful." The FDA's scientific and medical advisors were asked to vote on whether there was enough evidence that the single study with positive results could be accepted as primary evidence of effectiveness of Aduhelm for the treatment of Alzheimer's disease. Ten members of the Advisory Committee voted that the evidence was not sufficient, and one member voted that they were uncertain. Their comments were consistent with the statistical analysis provided by FDA scientists and statisticians, which pointed out that the drug is not proven to work and has substantial risks.

Although Biogen urged the FDA to ignore the conflicting findings and approve the drug based on the one study showing a slight but not clinically meaningful benefit, the FDA statistician pointed out that this was not scientifically appropriate, and the FDA Advisory Committee members agreed. They urged the FDA to refuse to approve the drug at this time and instead to encourage the company to conduct a well-designed third study that could confirm or refute previous findings. That would have been the wise choice, with the focus on determining if any patients benefit in a meaningful way, and if so, which types of patients are most likely to benefit and which patients are likely to be harmed. Instead, the FDA has made a decision that seems to have been based on lobbying pressure and wishful thinking, not on science. Three of the nine permanent voting members of the FDA's scientific Advisory Committee have publicly resigned as a result. The FDA's approval of Aduhelm on June 7 is not a scientifically appropriate FDA decision, and it sets a dangerous precedent for future treatments for Alzheimer's disease and all other treatments reviewed by the FDA. Since the results of the two studies of cognitive damage conflicted with each other, the FDA decided to ignore those results and instead focus on the biomarker of a substance in the brain called amyloid beta, which causes plaques on the brain. Although it is well known that amyloid beta is associated with Alzheimer's disease, reducing the substance has never been shown to improve memory, as an article published in the British Medical Journal explains.[1]

FDA law requires that approval decisions for prescription drugs be based on evidence that the benefits outweigh the risks. Aduhelm often causes brain swelling, which can cause headaches, falling, diarrhea, confusion and delirium/altered mental status. In other words, the scientific evidence indicates that there are no proven benefits, but there are proven risks. The FDA is requiring Biogen to continue to study their drug, but the study is not required to be completed until 2029, with an FDA review of those

data scheduled for completion in 2030. Unfortunately, the track record for post-market studies is one with frequent delays: in the study design, in recruiting patients, in completing the studies, and in analyzing data. How many patients will be exposed to a drug with unproven benefits and proven harms in the meantime?

FDA also ignored scientific standards in their decision to approve Aduhelm for all Alzheimer's patients, even though it was only studied on patients with mild Alzheimer's disease. This broad approval is especially questionable because there is scientific evidence that the more plaque on patients' brains (which is related to more severe stages of the disease), the worse the brain swelling is likely to be. That raises additional questions about whether the unknown benefits outweigh the known risks.

We've learned in recent years that the failure to "follow the science" can have devastating repercussions, and unfortunately this FDA decision is likely to wreak havoc on our healthcare system. Prescription drug coverage in the U.S. is almost entirely based on FDA approval, so the approval of a dangerous, unproven drug for approximately 6 million Americans will far exceed the amount Medicare spends on any other drug, according to Kaiser Family Foundation, straining Medicare's budget.[2] In addition to the drug costing $56,000 per patient per year, expensive PET scans and MRIs to test for amyloid plaques and monitor brain swelling side effects will add to the costs for anyone prescribed this drug. Since the Medicare trust fund is already expected to run out of money in 2024,[3] this one drug approval could result in a breakdown of healthcare for all Americans who are over the age of 65 or have chronic disabilities. In addition, patients using Aduhelm are estimated to have a co-pay of at least $11,500 for the drug alone, not including the necessary scans – and that is almost half of the average income of Medicare beneficiaries.[2] That steep out-of-pocket cost will put the drug out of reach for many of those with fewer resources, or result in families selling their homes or making other life-changing sacrifices. By ignoring the advice of its scientific advisors and making a decision without appropriate evidence, FDA is placing hundreds of thousands of patients at risk of serious harm, imperiling the Medicare budget, and making both financial strain and deepened inequity likely for millions of Medicare beneficiaries with Alzheimer's – all for a drug that is not proven to have clinically meaningful benefits.

When FDA approves a drug, the options for rescinding approval are time-consuming. Nevertheless, there are legal options to reduce the number of patients harmed. We make the following recommendations:

The FDA should revise the drug indication to be based on scientific evidence for mild Alzheimer's only and require well-designed confirmatory scientific studies within two years rather than nine years.

The Centers for Medicare and Medicaid Services (CMS) should ensure that Medicare uses appropriate scientific standards for its coverage decisions, regardless of lobbying pressure, even if those standards are not consistent with FDA's unscientific approval decision.

The Department of Health and Human Services Office of Inspector General should investigate whether the Aduhelm approval decision was consistent with FDA's scientific integrity policies and other agency standards, and determine whether policy changes are necessary to ensure that future drug approval decisions are not based on surrogate endpoints when meaningful clinical endpoints do not show benefit.

Thank you for your attention to this urgent matter. We urge that these steps be implemented as soon as possible, to protect the health of patients and to protect the scientific integrity of FDA and CMS.

If you have any questions, please contact Dr. Diana Zuckerman at dz@center4research.org.

Sincerely,

Government Accountability Project

Government Information Watch

Jacobs Institute of Women's Health

National Center for Health Research

National Women's Health Network

Union of Concerned Scientists

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