Congress of the United States
House of Representatives
Washington, D.C. 20515

January 13, 2022

The Honorable Chiquita Brooks-LaSure
Administrator
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Dear Administrator Brooks-LaSure:

We write to commend the Centers for Medicare & Medicaid Services (CMS) on its recently released proposed National Coverage Determination (NCD) decision memo for Aduhelm, a treatment for Alzheimer's disease, and other similar drugs. We applaud the agency for striking a balance between the need for Alzheimer's patients to access treatment with the need to gather more evidence on the treatment's safety and efficacy through clinical trials. Since receiving accelerated approval from the U.S. Food and Drug Administration (FDA) in June 2021, Aduhelm's approval process and its imbalance of benefit to risk have been met with concern from the scientific and medical communities.[1] In response to these widespread concerns, the Committee on Energy and Commerce and the Committee on Oversight and Reform launched a joint investigation into FDA's approval of Aduhelm and the role its developer, Biogen, played in that process.[2]

In addition to these concerns, the exorbitant price of Aduhelm—initially set by Biogen at $56,000 per year and recently reduced to $28,200 per year—is further cause for alarm.[3] We applaud Department of Health and Human Services (HHS) Secretary Becerra's call for the

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[1] *Three Experts Have Resigned from an FDA Committee Over Alzheimer's Drug Approval*, National Public Radio (June 11, 2021) (www.npr.org/2021/06/11/1005567149/3-experts-have-resigned-from-an-fda-committee-over-alzheimers-drug-approval); *Two Members of an FDA Advisory Committee Quit After Approval of Controversial Alzheimer's Drug*, The Washington Post (June 9, 2021); *How an Unproven Alzheimer's Drug Got Approved*, The New York Times (July 19, 2021).

[2] Committee on Oversight and Reform And Committee on Energy and Commerce, *Remarks as Prepared for Delivery by Chairwoman Carolyn B. Maloney, Committee on Oversight and Reform, and Chairman Frank Pallone, Jr., Committee on Energy and Commerce* (June 25, 2021).

[3] *Alzheimer's Drug is Bonanza for Biogen, Most Likely at Taxpayer Expense*, New York Times (June 8, 2021) ; Biogen, Inc., *Biogen Announces Reduced Price for Aduhelm to Improve Access for Patients with Early Alzheimer's Disease* (Dec. 20, 2021) (press release).

agency to reassess the Medicare Part B premium for 2022.[4] In light of both Aduhelm's price reduction and the recently proposed coverage with evidence NCD, it is critical that the agency reevaluate the assumptions used to determine the 2022 premium as soon as possible and work to reduce the premium for Part B beneficiaries.[5]

With the number of people living with Alzheimer's disease in the United States projected to increase from six million people today to as many as 14 million people by 2060, we are committed to supporting the development of new treatments.[6] In the effort to advance brain health equity and eradicate this devastating disease, it is vital that treatments be effective, safe, and accessible. Given the controversy surrounding Aduhelm—including its unusually high price, questionable efficacy, and known safety concerns—we urge CMS to finalize its NCD for approved monoclonal antibodies that target amyloid for the treatment of Alzheimer's disease as proposed, so that Medicare coverage for such drugs is provided only within the context of qualifying clinical trials.[7]

FDA's June 7, 2021 accelerated approval of Aduhelm was met with surprise and concern from a wide swath of experts.[8] Questions regarding the drug's approval process stem from the halt of its Phase 3 clinical trials in March 2019 based on the determination that the studies were futile due to a lack of meaningful results.[9] Yet on July 7, 2020, after a re-examination of the trial data and discussions with the FDA, Biogen submitted an application for approval to the agency.[10] At the November 6, 2020, meeting of the Peripheral and Central Nervous System

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[4] *Becerra asks Medicare to rethink 2022 premiums, citing Alzheimer's drug cost*, Politico (Jan. 10, 2021).

[5] Memorandum from Centers for Medicare and Medicaid Services, National Coverage Analysis (NCA) Proposed Decision: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (Jan. 11, 2021).

[6] Centers for Disease Control and Prevention, *Minorities and Women at Greater Risk for Alzheimer's Disease* (www.cdc.gov/aging/publications/features/Alz-Greater-Risk.html) (accessed Aug. 27, 2021).

[7] *See* note 4.

[8] *The FDA's Approval of Aduhelm: Potential Implications Across a Wide Range of Health Policy Issues and Stakeholders*, Health Affairs Blog (June 10, 2021) (www.healthaffairs.org/do/10.1377/hblog20210609.921363/full/); *Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug*, The New York Times (June 10, 2021).

[9] Biogen Inc., *Biogen and Eisai to Discontinue Phase 3 ENGAGE and EMERGE Trials of aducanumab in Alzheimer's Disease* (Mar. 21, 2019) (press release).

[10] Letter from Billy Dunn, Director, Office of Neuroscience, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, to Priya Singhal, Vice President, Global Safety and Regulatory Sciences, Biogen Inc. (June 7, 2021); Biogen, Inc., *Biogen Plans Regulatory Filing for Aducanumab in Alzheimer's Disease Based on New Analysis of Larger Dataset from Phase 3 Studies* (Oct. 22, 2019) (press release).

Drugs Advisory Committee (PCNS Advisory Committee), members voted on the question of whether the trial data on Aduhelm provided "primary evidence of effectiveness of [Aduhelm] for the treatment of Alzheimer's disease."[11] There was near consensus that it did not—10 of the 11 members voted "no," with one voting "uncertain."[12]

Following Aduhelm's approval, three PCNS Advisory Committee members resigned in protest, with one stating that "[t]his might be the worst approval decision that the FDA has made that I can remember."[13] Former Biogen employees and health care providers, among others, also voiced strong opposition to Aduhelm's approval, amid concerns around safety and efficacy.[14] In the months following FDA's approval, several major medical centers, including the Cleveland Clinic, Mount Sinai, and Mass General Brigham decided not to administer Aduhelm to their patients after their respective experts balanced the known safety risks with the lack of evidence of efficacy.[15] Additionally, Blue Cross Blue Shield plans in multiple states announced that they would not cover the drug.[16] The Department of Veterans Affairs (VA) followed suit, making the determination not to add Aduhelm to the VA National Formulary "due to the risk of significant adverse drug events and to the lack of evidence of a positive impact on cognition."[17] Further, a recent survey found that at least 15 university-affiliated hospitals are not offering the drug.[18]

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[11] U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *Final Summary Minutes of the Peripheral and Central Nervous System Drugs, Advisory Committee Meeting* (Nov. 6, 2020) (www.fda.gov/media/145690/download).

[12] *Id.*

[13] *Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug*, The New York Times (June 10, 2021).

[14] *How an Unproven Alzheimer's Drug Got Approved*, The New York Times (July 19, 2021).

[15] *Cleveland Clinic and Mount Sinai Won't Administer Aduhelm to Patients*, The New York Times (July 14, 2021); *Mass General Brigham vetoes Controversial Alzheimer's drug Aduhelm after internal review*, Fierce Healthcare (www.fiercehealthcare.com/hospitals/mass-general-brigham-vetoes-controversial-alzheimer-s-drug-aduhelm-after-internal-review) (Accessed Jan. 13, 2022).

[16] *Some Blues Plans Won't Cover New Alzheimer's Therapy Aduhelm*, Formulary Watch (www.formularywatch.com/view/some-blues-plans-won-t-cover-new-alzheimer-s-therapy-aduhelm) (Accessed Jan. 13, 2022).

[17] *Scoop: VA decides against adding Biogen's Aduhelm to its formulary as PBM shuns controversial Alzheimer's drug*, EndPoints News (Aug. 11, 2021) (www.endpts.com/exclusive-va-decides-against-adding-biogens-aduhelm-to-its-formulary-as-pbm-shuns-controversial-alzheimers-drug/).

[18] *'It's almost negligible': More top hospitals aren't offering controversial Alzheimer's drug Aduhelm*, Stat (Jan. 6, 2021) (www.statnews.com/2022/01/06/top-hospitals-arent-offering-aduhelm/).

Among three academic hospitals that did add Aduhelm to their formularies, their providers are only treating patients with Aduhelm within a clinical trial.[19]

Much of the controversy surrounding Aduhelm's approval is centered on FDA's position that clinical trial data demonstrated the drug reduced the buildup of amyloid beta plaque in the brain.[20] Despite internal concerns regarding the "inconsistency" of the drug's supporting clinical data, FDA determined that the reduction of amyloid beta plaque serves as a surrogate endpoint that is "reasonably likely to predict a clinical benefit to patients" of delaying cognitive decline.[21] FDA has used surrogate endpoints to grant accelerated approval for drugs for other diseases and conditions, including for cancer and HIV.[22] Unlike the surrogate endpoints relied upon for those other treatments, however, there is not consensus among medical and neurological experts that the reduction in amyloid plaque is a surrogate endpoint reasonably likely to demonstrate clinical benefit.[23]

In fact, experts have noted that the link between reduction of amyloid beta plaque and slowing cognitive decline for Alzheimer's patients "is not well-established and has even been questioned."[24] Additionally, in a critique of FDA's Aduhelm approval, seven of the PCNS Advisory Committee members—including the three who resigned in protest following Aduhelm's approval—stated that, "[t]o date, clinical trials provide no substantial evidence that lowered beta-amyloid predicts clinical benefit."[25] These experts also pointed out that prior to Aduhelm's approval, "FDA had not indicated that it considered beta-amyloid a valid pharmacodynamic biomarker, much less an acceptable surrogate endpoint for clinical trials."[26] Indeed, FDA's most recent draft guidance, published in February 2018, *Early Alzheimer's*

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[19] *Id.*

[20] U.S. Food and Drug Administration, *FDA Grants Accelerated Approval for Alzheimer's Drug* (June 7, 2021) (press release).

[21] U.S. Food and Drug Administration, Center for Drug Evaluation Research, *Application Number: 761178Orig1s000, Statistical Review(s)* (July 7, 2020) (www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000StatR_Redacted.pdf); *See* note 14.

[22] U.S. Food and Drug Administration, *Development and Approval Process – Drugs* (www.fda.gov/drugs/development-approval-process-drugs) (Accessed Jan. 13, 2022).

[23] Vincent Planche and Nicolas Villain, *US Food and Drug Administration Approval of Aducanumab—Is Amyloid Load a Valid Surrogate End Point for Alzheimer Disease Clinical Trials?* JAMA Neurology (Sept. 13, 2021).

[24] *Insights on FDA's Controversial Approval of Alzheimer's Drug*, Johns Hopkins University Hub (June 21, 2021).

[25] *See* note 9; G. Caleb Alexander et al., *Revisiting FDA Approval of Aducanumab*, The New England Journal of Medicine (Aug. 26, 2021).

[26] G. Caleb Alexander et al., *Revisiting FDA Approval of Aducanumab*, The New England Journal of Medicine (Aug. 26, 2021).

Disease: Developing Drugs for Treatment, Guidance for Industry, notes that for early Alzheimer's disease trials in Stage 1 patients, "there is unfortunately at present no sufficiently reliable evidence that any observed treatment effect on such biomarker measures would be reasonably likely to predict clinical benefit."[27] In correspondence to the Committees, FDA indicated that revisions are planned to this guidance, and that updated guidance is expected by 2023.[28]

Beyond the uncertainty regarding Aduhelm's potential to demonstrate clinical benefit, there is conclusive evidence of safety risks. According to a secondary analysis of Aduhelm's two late-stage trials, more than 41 percent of the patients with early Alzheimer's taking Aduhelm in the Phase 3 studies had amyloid-related imaging abnormalities (ARIA), such as brain swelling or microbleeds.[29] One-quarter of these patients experienced related symptoms including headache, confusion, dizziness and nausea.[30] Compounding these concerns, a woman participating in the drug's ongoing studies died in late September 2021.[31] While she presented with progressively severe ARIA which led to epilepticus (seizure), any direct connection between Aduhelm and her death is unknown.[32] FDA and Biogen continue to conduct their own respective investigations into her death.[33]

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[27] U.S. Food and Drug Administration, *Early Alzheimer's Disease: Developing Drugs for Treatment, Guidance for Industry* (Feb. 2018) (www.fda.gov/media/110903/download) (as defined in FDA's guidance, Stage 1 patients are those "with characteristic pathophysiologic changes of AD but no evidence of clinical impact").

[28] Letters from Andrew Tantillo, Acting Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to Rep. Frank Pallone, Jr., Chairman, House Committee on Energy and Commerce, and Rep. Carolyn B. Maloney, Chairwoman, House Committee on Oversight and Reform (Oct. 22, 2021); Information provided by U.S. Food and Drug Administration to the Committee on Energy and Commerce and House Committee on Oversight and Reform on Jan. 3, 2022.

[29] Stephen Salloway et al., *Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease*, JAMA Neurology (Nov. 22, 2021).

[30] *Id*.

[31] *ARIA Side Effects Surface in 40% of Patients on Biogen's Alzheimer's Drug Aduhelm: JAMA*, Fierce Pharma (Nov. 23, 2021).

[32] *Id.*

[33] *Exclusive: FDA probing death of Aduhelm patient as Biogen's Alzheimer's drug continues to stir controversy*, Endpoints News (Nov. 18, 2021) (endpts.com/rbc-analyst-reports-aducanumab-case-file-points-to-the-controversial-alzheimers-drug-as-a-likely-cause-of-patient-death/) (assessed Jan. 13, 2022); *Biogen Investigates Death of 75-Year-Old on Aduhelm*, BioSpace (Nov. 10, 2021) (www.biospace.com/article/biogen-investigates-death-in-75-year-old-alzheimer-s-patient-on-aduhelm/) (accessed Jan 13, 2022).

Many experts have also challenged the unreasonably high price of Aduhelm, originally set by Biogen at $4,312 per infusion for an estimated price of $56,000 per year.[34] In August, for example, the Institute for Clinical and Economic Review (ICER) released its final evidence report on the effectiveness and value of Aduhelm for treatment of Alzheimer's, stating that the appropriate price range based on the projected benefit would be $3,000–$8,400 per year because it found "the current evidence to be insufficient to demonstrate that aducanumab [Aduhelm] slows cognitive decline, while it is clear that it can harm some patients."[35] On December 20, 2021, Biogen announced that it will be reducing the price of Aduhelm by approximately 50 percent.[36] Even with this reduction, the company estimated that the average yearly maintenance dosing for its drug would be $28,200 per year—a price still more than three times the highest cost recommended by ICER.[37]

As you know, the excessive price of Aduhelm has already led to a significant increase in Medicare Part B premiums as a contingency in case the decision is made to cover the drug under Part B.[38] On November 12, 2021, CMS announced a $21.60 increase to Medicare Part B premiums for 2022, in significant part due to "uncertainty regarding the potential use of the Alzheimer's drug, Aduhelm."[39] According to reporting, a CMS official indicated that Aduhelm's initial price is responsible for nearly $10 of this amount.[40] Additionally, as noted above, major medical systems and hospitals have been reticent to offer or cover the treatment, leading to limited use of the drug. According to reporting, the "organization that negotiates supply contracts on behalf of more than 95 percent of the nation's academic hospitals estimates

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[34] *Biogen Alzheimer's Drug Will Exceed the $56,000 List Price for Many, Analysis Says*, The Wall Street Journal (July 9, 2021); *Biogen's $56K Price on Aduhelm 'Simply Unacceptable,' Alzheimer's Association Says After Vouching for FDA Approval*, Fierce Pharma (June 14, 2021) (www.fiercepharma.com/pharma/biogen-s-56k-price-tag-for-aduhelm-simply-unacceptable-and-needs-fixed-alzheimer-s).

[35] Institute for Clinical and Economic Review, *ICER Publishes Final Evidence Report and Policy Recommendations on Aducanumab for Alzheimer's Disease* (Aug. 5, 2021) (press release).

[36] Biogen, Inc., *Biogen Announces Reduced Price for Aduhelm to Improve Access for Patients with Early Alzheimer's Disease* (Dec. 20, 2021) (press release).

[37] *Id.*

[38] *Alzheimer's Drug Cited as Medicare Premium Jumps by $21.60*, Associated Press (Nov. 12, 2021).

[39] Centers for Medicare and Medicaid Services, *2022 Medicare Parts A & B Premiums and Deductibles/2022 Medicare Part D Income-Related Monthly Adjustment Amounts (https://www.cms.gov/newsroom/fact-sheets/2022-medicare-parts-b-premiums-and-deductibles2022-medicare-part-d-income-related-monthly-adjustment)*.

[40] *Aduhelm, priced at $56,000 a year, is a key factor driving up Medicare premiums*, CNN (Nov. 16, 2021).

their members are ordering just one to five vials of the medicine each day."[41] Given Biogen's decision to nearly halve Aduhelm's price since CMS calculated the 2022 Medicare Part B premium, evidence of limited uptake of the drug, and the proposed NCD, we strongly support Secretary Becerra's January 10, 2022, order for CMS to reassess the premium, and we encourage the agency to do so expeditiously.

Despite the continued controversy, FDA's reliance on the surrogate endpoint to grant accelerated approval for Aduhelm has opened the pathway to other drug companies seeking approval for their similar Alzheimer's drug candidates. Biogen's Japanese partner in Alzheimer's research, Eisai, has already initiated a rolling submission for its drug, lecanumab, which was granted fast track designation in December.[42] Eli Lilly has also announced it has begun filing a rolling submission for FDA approval for donanemab, its Alzheimer's drug candidate.[43]

Aduhelm's approval process has also raised questions regarding the unique communication and level of coordination between FDA and Biogen. As noted above, this process is currently under investigation by our respective Committees, as well as the HHS Office of the Inspector General (OIG). FDA and Biogen continue to cooperate with the Committees' investigation. However, serious questions and concerns remain surrounding the approval process for Aduhelm. Our Committees will continue to diligently and aggressively investigate Aduhelm's approval process. The Committees' work here is especially critical as the HHS OIG investigation—which was initiated at FDA Acting Commissioner Janet Woodcock's request and will assess "how the FDA implements the accelerated approval pathway" and "interactions between the FDA and outside parties as well as other aspects of the process, such as deciding on this pathway and scientific disputes"—is not anticipated to be complete until 2023 and may result in multiple reports.[44]

In the meantime, although many questions remain unanswered, CMS is charged with independently determining if Aduhelm is "reasonable and necessary" for Medicare

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[41] *'It's almost negligible': More top hospitals aren't offering controversial Alzheimer's drug Aduhelm*, STAT News (Jan. 6, 2021) (www.statnews.com/2022/01/06/top-hospitals-arent-offering-aduhelm/).

[42] Eisai Co. Ltd., *Eisai Initiates Rolling Submission to the U.S. FDA for Biologics License Application of Lecanemab (BAN2401) for Early Alzheimer's Disease Under the Accelerated Approval Pathway* (Sept. 28. 2021) (press release); *Lecanemab granted fast track designation by the FDA*, PRNewswire (Dec. 24. 2021) (www.prnewswire.com/news-releases/lecanemab-granted-fast-track-designation-by-the-fda-301450656.html).

[43] Eli Lilly and Company, *Lilly Reports Robust Third-Quarter 2021 Financial Results as Pipeline Success Strengthens Future Growth Potential* (Oct. 26, 2021) (news release).

[44] U.S. Department of Health and Human Services, Office of the Inspector General, Review of the FDA's Accelerated Approval Pathway (oig.hhs.gov/reports-and-publications/workplan/summary/wp-summary-0000608.asp) (accessed Dec. 15, 2021).

beneficiaries.[45] While Medicare does cover the majority of FDA-approved drugs, FDA approval does not guarantee Medicare coverage.[46] Over the past decade, CMS has routinely required that interventions demonstrate improved patient health outcomes—and not just surrogate endpoints—particularly among Medicare beneficiary populations.[47] Given that Aduhelm's approval has ushered in new drug candidates seeking to capitalize on the same surrogate endpoint to gain accelerated approval, CMS's coverage determination for monoclonal antibodies targeting amyloid for the treatment of Alzheimer's disease will have far-reaching implications for millions of patients for years to come.

We commend CMS for its evidence-based approach in developing this proposed NCD and weighing Aduhelm's established potential for patient harm, its inconclusive potential for patient benefit, and the needs of patients, clinicians, and caregivers. This determination will allow certain Alzheimer's patients access to Aduhelm while providing the opportunity to gain more evidence on the drug's efficacy and safety. Any broader coverage determination before there is clarity on Aduhelm's approval process and findings from the myriad ongoing investigations may put the health of millions of Alzheimer's patients on the line and the financial stability of the nation's health insurance program for American seniors at risk.

Sincerely,

Frank Pallone, Jr.
Chairman
Committee on Energy and Commerce

Carolyn B. Maloney
Chairwoman
Committee on Oversight and Reform

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[45] 42 U.S.C. § 1395y; James D. Chambers et al., *Medicare Covers the Majority of FDA-Approved Devices and Part B Drugs, but Restrictions and Discrepancies Remain*, Health Affairs (June 2013).

[46] James D. Chambers, Katherine E. May, and Peter J. Neumann, *Medicare Covers the Majority of FDA-Approved Devices and Part B Drugs, but Restrictions and Discrepancies Remain*, Health Affairs (June 2013); James D. Chambers et al., *Medicare 'Coverage with Evidence Development' for Aducanumab? How Might it Work?*, Health Affairs (June 30, 2021).

[47] James D. Chambers et al., *Medicare 'Coverage with Evidence Development' for Aducanumab? How Might it Work?* Health Affairs (June 30, 2021); Peter J. Neumann and Sean R. Tunis, *Medicare and Medical Technology — The Growing Demand for Relevant Outcomes*, The New England Journal of Medicine (Feb. 10, 2010).

cc: The Honorable Xavier Becerra
Secretary
Department of Health and Human Services

Mr. Paul Spitalnic
Director and Chief Actuary
Office of the Actuary
Centers for Medicare & Medicaid Services