Comments Prepared for the Centers for Medicare and Medicaid Services' Listening Session Regarding the National Coverage Determination Analysis for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N)

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The Food and Drug Administration's (FDA's) decision to approve aducanumab for treatment of Alzheimer's disease showed a stunning disregard for science and eviscerated the agency's standards for approving new drugs. Because of this reckless action, the agency's credibility has been irreparably damaged.

The approval of aducanumab was based on seriously flawed post hoc analyses of two identical phase 3 trials that were stopped early because a preliminary review of the data found that the trials, if continued to completion, were unlikely to show the drug benefitted Alzheimer's patients. Moreover, the integrity of the FDA's review of the marketing application for aducanumab was dangerously corrupted by the unprecedented and inappropriately close collaboration between Biogen and the FDA during the analyses of data from the key clinical trials of the drug after the termination of the phase 3 clinical trials because of futility.

The Centers for Medicare and Medicaid Services (CMS) must not compound the FDA's egregious error in approving aducanumab on June 7th. Given the lack of scientific evidence that aducanumab provides any meaningful clinical benefit in terms of cognitive function outcomes in Alzheimer's disease patients, the drug cannot possibly be deemed reasonable and necessary for treatment of such patients. Public Citizen therefore urges CMS to issue a National Coverage Determination that excludes aducanumab from coverage under the Medicare program.

Regarding the first question posed by CMS in its request for comments — Which health outcomes are important, and what degree of improvement in them is meaningful for patients receiving treatment? — based on the currently available scientific evidence, reduction of amyloid-beta plaques in the brain itself is not a clinically meaningful outcome for Alzheimer's disease patients and is not sufficient for establishing a drug as being reasonable and necessary for treatment of such patients.

The FDA approved aducanumab for treatment of Alzheimer's disease under its Accelerated Approval pathway based on an unvalidated surrogate endpoint — reduction of amyloid-beta plaques in the brain. In her June 7, 2021, statement announcing the FDA's approval decision, Dr. Cavazzoni asserted that "reduction in [brain amyloid-beta] plaques — a hallmark finding in the brain of patients with Alzheimer's — is expected to lead to a reduction in the clinical decline of this devastating form of dementia." However, the currently available evidence — including evidence from the clinical trials of aducanumab itself — fails to show a correlation between changes in this surrogate endpoint and changes in clinical measures of cognitive function.

Like the nearly two dozen prior unsuccessful experimental drugs targeting amyloid-beta that were pursued as potential treatments for Alzheimer's disease over the past two decades, use of aducanumab is predicated on the still-unproven "amyloid hypothesis," which was introduced in the early 1990s and posits that deposition of amyloid-beta plaques in the brain causes the neuronal degeneration seen in Alzheimer's disease. None of these drugs was shown to be efficacious for treating Alzheimer's disease — including some drugs that were shown to prevent further accumulation of amyloid-beta plaques in the brain or to reduce the amount of amyloid-beta plaques in the brain based on positron emission tomography scans — and many caused serious harm, including worsening of cognition in some cases.

Most germane, although the clinical trials of aducanumab demonstrated amyloid-beta reductions that were greater than those observed for some prior drugs that targeted amyloid-beta, data from the two phase 3 clinical trials of aducanumab also found no significant correlation between the reductions in amyloid-beta plaques in the brain and changes in the primary clinical measure for cognitive function in subjects with Alzheimer's disease.

Health outcomes that would be important for patients receiving a drug treatment for Alzheimer's disease would be substantial slowing of declines on measures of cognitive function. Such clinically meaningful health outcomes must be demonstrated in large, randomized, placebo-controlled trials that have been completed and analyzed in accordance with prespecified statistical analysis plans described in the trial protocols. The phase 3 clinical trials for aducanumab utterly failed to meet these criteria.

In conclusion, Public Citizen urges CMS to issue a National Coverage Determination that excludes aducanumab from coverage under the Medicare program because there is a lack of scientific evidence that aducanumab provides any meaningful clinical benefit in terms of cognitive function outcomes in Alzheimer's disease patients and the drug thus is not reasonable and necessary for treatment of such patients.