Aducanumab: What Clinicians Should Know

(current as of July 16, 2021)

AGS Geriatrics Healthcare Professionals

Leading Change. Improving Care for Older Adults.

On June 7, 2021, the Food and Drug Administration (FDA), under its accelerated approval pathway, approved aducanumab (to be marketed under the name Aduhelm™) for use in treating patients with mild cognitive impairment or mild dementia stage of Alzheimer's disease. The FDA accelerated approval pathway is typically used for treatments for serious or life-threatening ailments that potentially offer a meaningful therapeutic advantage over existing treatments. Accelerated approval can be based on the drug's effect on a surrogate endpoint that is considered likely to predict important, but unmeasured, clinical outcomes. In the case of aducanumab, the FDA determined that the reduction of amyloid beta plaque in the brain—considered a surrogate endpoint that is an indicator of Alzheimer's disease—was sufficient to warrant approval with requirement of a post-approval clinical trial to confirm clinical benefit.

From the perspective of the American Geriatrics Society, what matters most to patients with Alzheimer's disease, their families, and other care partners is whether a proposed new treatment provides clear clinical benefits to cognitive and functional performance and other key outcomes. Available data are insufficient to answer this key question and aducanumab should be used with caution. Bottom line, we consider the evidence inconclusive when it comes to prescribing this drug.

At the same time, we recognize that with FDA approval of aducanumab, AGS members and other clinicians caring for older adults are being asked whether this new treatment is right for their patients. We have developed preliminary advice to help clinicians in assisting their patients and surrogates to be fully informed about the risks and benefits of this new treatment based on the available data.

PRESCRIBING ADUCANUMAB

Before prescribing, AGS recommends that clinicians review full prescribing information and know any prior authorization and other requirements for prescribing.

Based on our review of the available data, AGS recommends that clinicians only consider prescribing aducanumab after confirming the patient is a candidate for this treatment, informing them as to what is known about it, and discussing whether the potential clinical benefit outweighs the risks. Shared decision-making should reflect the following:

- Informing patients with a condition that meets the key exclusion criteria (see Table 1) that aducanumab was studied only in generally healthy people with mild cognitive impairment or mild dementia due to Alzheimer's disease. The studies did not include people with the types of health issues they may have (e.g., atrial fibrillation and on a blood thinner). There are no safety or efficacy data from the aducanumab studies for someone with these conditions.
- Informing people living with Alzheimer's disease and their loved ones about how aducanumab was studied and the basis of the FDA approval. Specifically, and importantly, it is not yet known whether treatments like aducanumab that remove amyloid from the brain produce clinically important slowing of cognitive or functional decline in Alzheimer's disease.

- Establishing, using validated staging tools, that the patient has mild cognitive impairment or mild dementia due to Alzheimer's disease. An example of a validated staging tool is the Clinical Dementia Rating (CDR) scale[1] which is used to assess dementia severity.
- Confirming that the patient has evidence of Alzheimer's disease, defined by a validated test to establish the presence of amyloid pathology. In the trials, a positive amyloid Positron Emission Tomograph (PET scan) was required.
- Informing patients about the cost of treatment (Biogen has indicated that the estimated cost of aducanumab will start at $56,000) and that there are additional costs related to how the drug is administered (by infusion), for ongoing monitoring of the brain via clinical assessment and MRI, and any additional medical care (including hospitalization) that may be necessary to deal with complications of treatment. Coverage may differ by payer, and this is an evolving landscape given that Medicare, Medicaid, and third-party insurers have not yet issued decisions as to what will be covered.
- Alerting patients that monthly infusions (approximately one hour in length) will be needed for 12 to 24 months or longer; and telling them where they will receive treatment (e.g., in the physician's office, at a health care center, or at another location).
- Alerting patients that they will need to obtain a baseline MRI (within one year prior to commencing treatment) and MRIs prior to the 7th and the 12th infusions.
- Having a plan in place for closely monitoring patients for potential side effects and adverse advents, including amyloid-related imaging abnormalities (ARIA). In the trials, if ARIA was found, treatment was suspended until it was resolved (see Table 1).
- Having a plan for closely monitoring cognition and function over time to assess whether the treatment is slowing cognitive decline. Given the lack of information on the matter, decisions about whether and when to discontinue the drug would be based on clinical judgment.

[1] The components of the CDR are Memory, Orientation, Judgement and Problem Solving, Community Affairs, Home and Hobbies, Personal Care. Each is graded from 0 to 3 based on the level of impairment (none to severe) as reported by the patient and a reliable informant.

SUMMARY OF WHAT WE KNOW ABOUT ADUCANUMAB

The Major Differences between the FDA Approval and the Trials

Clinicians should know that the FDA approval of aducanumab differs significantly from what was studied in the trials as highlighted in Table 1 below.

	FDA Label	Clinical Trials (ENGAGE, EMERGE)
Population	Aduhelm™ is indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. The label does not specify contraindications.	Aducanumab was only studied in people who had: ■ A positive amyloid positron emission tomograph (PET scan); AND ■ Mild cognitive impairment or mild dementia due to Alzheimer's disease. A total of 1105 patients received aducanumab 10 mg/kg. 52% were women, 76% were White, 10% were Asian, and 3% were of Hispanic or Latino ethnicity. The mean age at study entry was 70 years (range from 50 to 85). Individuals with dementia stages earlier or later than 'mild' were not studied.

Table 1: Differences between what FDA Approved and what was Studied / continued

	FDA Label	Clinical Trials (ENGAGE, EMERGE)
Contraindications/ Trial Exclusion Criteria	The label does not specify contraindications	Patients were excluded from the clinical trial if they met any of the following exclusion criteria: 1. Over the age of 85 2. Any uncontrolled medical condition 3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to screening 4. Brain MRI performed at screening that shows evidence of any of the following: acute or sub-acute hemorrhage, prior microhemorrhage or prior subarachnoid hemorrhage (unless finding is not due to an underlying structural or vascular hemorrhage), more than 4 microhemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis or history of diffuse white matter disease. 5. Contraindications to having a brain MRI or PET scan 6. History of bleeding disorder 7. Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤325 mg daily) 8. Uncontrolled hypertension or history of unstable angina, myocardial infarction, chronic heart failure, or clinically significant conduction abnormalities
Determining level of cognitive impairment and presence of amyloid plaque	The label does not require any diagnostic tests before this drug is prescribed.	Before enrollment in either of the two trials, patients were required to undergo both an amyloid PET scan and detailed cognitive testing and staging.
Ongoing screening to assess benefit to patients	None	Patients underwent repeated PET scans and cognitive assessments during the trials.

Table 1: Differences between what FDA Approved and what was Studied / continued

	FDA Label	Clinical Trials (ENGAGE, EMERGE)
Screening and treatment protocol for adverse events	■ Obtain baseline MRI within one year prior to initiating treatment. ■ Obtain MRIs prior to the 7th and 12th infusions. ■ If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).	■ ARIA monitoring methods and data collection throughout the aducanumab clinical program included routine brain MRI scans performed for all participants at protocol-specified timepoints, follow-up MRI scans performed for participants in whom ARIA was detected, and a centralized MRI reader staffed with expert radiologists highly experienced with ARIA. ■ In the clinical trial, patients with ARIAs had aducanumab use suspended until they resolved. Follow-up brain MRIs for participants who developed ARIA were performed every 4 weeks until ARIA resolved (ARIA-E) or stabilized (ARIA-H).

WHAT CLINICIANS SHOULD KNOW

FDA Approval

- As of July 8, 2021, FDA had issued a revised approval for Aduhelm™ indicating that it should be used to treat patients with mild cognitive impairment or mild dementia stage of Alzheimer's disease. The FDA approved this new treatment under its fast-track pathway, acknowledging that the approval was based on a surrogate or intermediate clinical endpoint. In the case of aducanumab, the surrogate endpoint was reduction of amyloid plaque that remains in the brain.
- Factors other than amyloid influence risk for dementia, including genetic and non-genetic risk factors (e.g., certain medications, lifestyle, vascular disease, and environmental factors such as air pollution).
- Aducanumab was only studied in generally healthy people with a positive PET scan and with mild cognitive impairment OR mild dementia due to Alzheimer's disease. The FDA is not requiring diagnostic testing before prescribing, has not included any contraindications on the label, and has not specified detailed requirements for monitoring treatment.
- FDA is requiring Biogen to do a fourth randomized clinical trial to prove that aducanumab actually slows the progression of Alzheimer's disease measured in clinical results, not just in changes in visualized amyloid deposits.

About the Trials

- Aducanumab is a human monoclonal antibody developed by Biogen that was assessed in two identical phase III randomized placebo-controlled trials, ENGAGE and EMERGE, which were planned to provide 18-month outcome data in generally healthy patients who had a positive amyloid positron emission tomography (PET) scan AND mild cognitive impairment or mild dementia due to Alzheimer's disease. It was not studied in people with moderate or more severe Alzheimer's disease. Study participants were given either a low or high dose of the drug.
- Individuals enrolled in the pre-approval trials were generally healthy (see exclusion criteria in Table 1). Aducanumab has not been studied in patients on anticoagulation or anti-platelet therapy (other than aspirin <325 mg daily), either of which may significantly increase risk of treatment. The majority of trial participants were White, reflecting a lack of racial and ethnic diversity in the trial population. People over the age of 85 were excluded from participating in the trial and there are no data available on the percentage of trial participants who were Black.
- Thirty to forty percent of individuals developed "amyloid-related imaging abnormalities (ARIA)," a potentially serious adverse event that includes edema (swelling of brain tissue) and bleeding within or at the surface of the brain (called microhemorrhages or superficial siderosis). Patients may report headache, changes in mental state, confusion, vomiting, nausea, tremor, and gait disturbances. While ARIA findings can be asymptomatic, some cases are severe.
- At the half-way point (March 2019), both trials were terminated after a planned interim analysis by an independent data review committee met criteria for clinical futility. The analysis found no clinical benefit versus placebo. Further analysis of additional data, however, found conflicting data regarding efficacy between the two trials, with only one, EMERGE, showing a benefit in a sub-analysis of data from participants receiving the higher of the two doses studied.
- The two trials of aducanumab had different results with one trial (ENGAGE) showing no slowing of the progression of Alzheimer's disease at either the high or low dose, and the second (EMERGE) showing some slowing of decline only at higher doses.
- In addition to the baseline assessment, clinical measures were evaluated at 6 months, 1 year, and 18 months, amyloid PET was done at 6 months and 18 months, CSF and Tau PET assessments were done at 18 months, and MRI was done at 6 months and 18 months.
- Five clinical efficacy scales were selected to measure the broad array of symptoms experienced by individuals with Alzheimer's disease: CDR-SB, MMSE, ADAS-Cog13, ADCS-ADL-MCI, and NPI-10. The FDA endorsed a statistically significant effect on the CDR-SB as a clinically meaningful outcome. The secondary clinical efficacy measures (MMSE, ADAS-Cog13, and ADCS-ADL-MCI) were accepted as providing supportive information. All measures had as a primary endpoint the change from baseline at Week 78.
- Aducanumab treatment produced statistically significant, dose-dependent reductions in brain amyloid plaque versus placebo, as measured by PET, at both Weeks 26 and 78.
- B*ottom Line:*
  - Only the higher (10 mg/kg) dose used in the EMERGE trial showed a benefit on the Clinical Dementia Rating – Sum of Boxes (CDR-SB). The benefit was marginal.
  - It is not yet clear whether treatments like aducanumab that remove amyloid from the brain produce clinically important slowing of cognitive decline in Alzheimer's disease.

Cost and Coverage

- Biogen has indicated that the estimated cost of Aduhelm™ will start at $56,000. There are additional costs related to how the drug is administered (by infusion), for ongoing monitoring of the brain via clinical assessment and MRI, and any additional medical care (including hospitalization) that may be necessary to deal with complications of treatment.
- As of June 2021, Medicare, Medicaid, and third-party insurance coverage had not yet been approved.

ABOUT THE AGS

The American Geriatrics Society (AGS) is a nationwide, not-for-profit society of geriatrics healthcare professionals dedicated to improving the health, independence, and quality of life of older people. Our 6,000+ members include geriatricians, geriatrics nurse practitioners, social workers, family practitioners, physician assistants, pharmacists, and internists who are pioneers in advanced-illness care for older individuals, with a focus on championing interprofessional teams, eliciting personal care goals, and treating older people as whole persons.

We provide leadership to healthcare professionals, policymakers, and the public by implementing and advocating for programs in patient care, research, professional and public education, and public policy.

ACKNOWLEDGEMENTS

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The AGS Executive Committee reviewed and approved this document and made recommendations on behalf of the AGS Board of Directors on July 15, 2021.

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SUGGESTED READING

FDA Analysis

Aducanumab (marketed as Aduhelm™) Information https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information

November 6, 2020 BLA 761178: Peripheral and Central Nervous System Drugs Advisory Committee Meeting. Script for FDA Presentation: Aducanumab for the Treatment of Alzheimer's Disease: Clinical Overview of Efficacy. FDA Presenter: Kevin M. Krudys, PhD. https://www.fda.gov/media/143505/download

Aducanumab Advisory Committee Briefing Document https://fda.report/media/143503/PCNS-20201106-CombinedFDABiogenBackgrounder_0.pdf

Payment Policy

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Will Insurers Pay for New Alzheimer's Drug? MedPage Today, June 8, 2021. https://www.medpagetoday.com/special-reports/exclusives/92990

The FDA's Approval Of Aduhelm: Potential Implications Across A Wide Range Of Health Policy Issues And Stakeholders. Health Affairs Blog, June 10, 2021. DOI: 10.1377/hblog20210609.921363 https://www.healthaffairs.org/do/10.1377/hblog20210609.921363/full/

The Drug That Can Break American Health Care. The Atlantic, June 11, 2021. https://www.theatlantic.com/ideas/archive/2021/06/aduhelm-drug-alzheimers-cost-medicare/619169/

Peer-Reviewed Articles

Alexander GC, Emerson S, Kesselheim AS. Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility.

JAMA. 2021;325(17):1717–1718. doi:10.1001/jama.2021.3854 (requires subscription)