

Aducanumab: What You Should Know

(Based on available information as of September 24, 2021)

A lzheimer's disease is a brain disorder that destroys memory and thinking skills over time. It is the most common form of dementia in older adults. Today, some 5.3 million Americans live with Alzheimer's disease, and it is now the sixth leading cause of death in the United States. The number of older adults who will develop Alzheimer's disease is expected to more than triple by 2050.

The exact causes of Alzheimer's disease are not fully known, but some risk factors are recognized. Aging is the most important one. Others include genetics – you may be more likely to develop Alzheimer's disease if a family member was affected. Scientists are studying the relationship between problems with memory and thinking and other conditions such as high blood pressure, heart disease, stroke, and diabetes. Researchers have also been investigating how factors such as education, diet, and environment may play a role.

Like other chronic diseases, Alzheimer's has no cure. But much can be done to help people living with the disease and the family and friends who care for them. Some medications, such as donepezil (Aricept), galantamine (Razadyne) and rivastigmine (Exelon), can improve some symptoms. Other medications may help some individuals with Alzheimer's disease who are experiencing severe depression, anxiety, or changes in behavior. There are also many supportive services that can be provided to patients and their families to make living with Alzheimer's disease much easier. These include counseling and education, planned social activities, and taking breaks, among others.

■ **A great deal of research has been focused on discovering new medical treatments for Alzheimer's disease.** In June 2021, the Food and Drug Administration (FDA) approved a drug called **aducanumab (Aduhelm™)**. In July, the FDA narrowed aducanumab's approval to treating patients with mild cognitive impairment or mild dementia due to Alzheimer's disease. People with more advanced stages of dementia are not eligible for this treatment.

The FDA used a special type of evaluation in its decision, called an 'accelerated approval pathway.' This allows patients with serious or life-threatening diseases access to a drug if there is hope of improvement—even if there is still uncertainty about the drug's benefits to patients. Accelerated approval can be granted when a drug affects a "surrogate endpoint." This means that a drug can get approval if it improves something that *could* eventually lead to patient benefit, but it isn't the same thing as directly leading to benefits.

■ **In Alzheimer's disease, the surrogate endpoint considered by the FDA is the removal of a protein called amyloid from the brain.** Abnormal amyloid build up is considered a "marker" of Alzheimer's disease. We do not yet know if reducing amyloid in the brain will benefit patients either by reducing Alzheimer's disease symptoms, or helping to sustain brain function over time.

■ **Because it's uncertain whether or how much aducanumab might help patients, the FDA is requiring Biogen, its manufacturer, to do an additional clinical trial.** This study is currently being designed, and intended to see whether aducanumab slows the progression of Alzheimer's disease when are measured by direct benefits to patients, not just by changes in a surrogate endpoint (brain amyloid deposits). Biogen has indicated that the study could take up to nine years to produce results.

We consider the evidence inconclusive when it comes to prescribing this drug and believe that aducanumab should be used with caution.

What this Means for You and Your Physician

From the perspective of the American Geriatrics Society, what matters most to people with Alzheimer's disease, their families, and their health team is whether a proposed new treatment offers clinical benefits that help them function better. Right now, we simply don't have enough scientific information to know whether aducanumab will slow cognitive decline and preserve function for those who receive this treatment. Importantly, we do not yet know whether treatments like aducanumab that remove amyloid from the brain can slow or prevent cognitive or functional decline in Alzheimer's disease.

For these reasons, we consider the evidence inconclusive when it comes to prescribing this drug and believe that aducanumab should be used with caution.

At the same time, we recognize that with FDA approval of aducanumab, patients and families are interested in finding out whether this new drug is right for them or their loved ones. We have developed preliminary advice to help inform you about the risks and benefits of this new treatment based on the available data.

What You Should Know about aducanumab

There are differences between what the FDA approved and how aducanumab was studied and Tables 1 and 2 below compare those differences. Patients and caregivers considering aducanumab should know:

- **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 over the age of 85. They also did not include people with common types of health issues you may have (such as atrial fibrillation, bleeding disorders, heart failure, previous heart attack or stroke, brain hemorrhages, or any uncontrolled medical condition, such as high blood pressure). People taking a blood thinner were not studied. There is no information about the safety or effectiveness of aducanumab for a person with any of these conditions.
- **Aducanumab has potential side effects.** In the studies, 30-40% of study participants developed "amyloid-related imaging abnormalities" (ARIA). These are changes seen in the brain using Magnetic Resonance Imaging (MRI) scans. ARIA can be a potentially serious adverse event that causes swelling of brain tissue (edema) 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 trouble with walking. While ARIA seen on MRI scans may not cause any symptoms, some cases are severe. In the trials, if ARIA was found, treatment was discontinued until it was resolved and/or dosages were changed.

Diagnosis: Determining if aducanumab is right for you

AGS has advised clinicians who are considering prescribing aducanumab to:

- **Confirm that a patient's difficulties represent mild cognitive impairment (decline in cognitive function without major effects on everyday functioning) or mild dementia due to Alzheimer's disease.** An example of tests that help clinicians to confirm this is the [Clinical Dementia Rating \(CDR\) Scale](#), a way of measuring severity. The CDR assesses key areas of brain function including memory, judgement and problem solving, and everyday life in the community and at home, including hobbies and personal care. Each area is graded from 0 to 3 based on the level of impairment (none to severe) as reported by the patient and someone who knows the patient well. Other measures based on the CDR can be used to 'stage' cognitive decline (that is, establish its severity).
- **Obtain confirmation that the patient has evidence of beta amyloid plaque in the brain.** In the aducanumab studies, researchers required a positive amyloid [Positron Emission Tomography](#) (PET scan). Alternatively, a spinal tap (lumbar puncture) can be done so that the levels of amyloid proteins in the cerebrospinal fluid can be measured.
- **Obtain a baseline brain MRI** (within one year prior to beginning treatment).
- **Fully inform patient and caregivers as to what is known about aducanumab including potential harms and benefits of treatment.** Discuss what matters to patients and whether aducanumab is the right treatment for them.

Table 1: Diagnosis: Differences between what FDA Approved and what was Studied

FDA Approved Use	Clinical Trials (ENGAGE, EMERGE)
Population	
<p>Aducanumab, marketed as Aduhelm™ is indicated for the treatment of Alzheimer’s disease.</p> <p>Treatment with Aduhelm™ should be used only in Alzheimer’s patients who have mild cognitive impairment or mild dementia. This is the group who received the drug in clinical trials. It is the only group we have any information on about how safe or effective Aduhelm™ might be. We have no information about its use at later stages of the disease because this was not studied.</p>	<p>This drug was only studied in people who had:</p> <p>A positive amyloid positron emission tomography (PET scan);</p> <p>AND</p> <p>Mild cognitive impairment or mild dementia due to Alzheimer’s disease.</p> <p>A total of 1105 patients received doses of aducanumab based on their body weight. 52% were women, 76% were White, 10% were Asian, and 3% were of Hispanic or Latino ethnicity. Participants in the study were around 70 years old, with ages ranging from 50 to 85. People with dementia in earlier or later than ‘mild’ stages were not studied.</p>
Contraindications and Trial Exclusion Criteria	
<p>The FDA does not specify individuals or groups who should not receive this treatment.</p>	<p><u>Patients were excluded from the clinical trial if they met any of the following exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Over the age of 85 2. Any uncontrolled medical condition 3. Transient ischemic attack (TIAs or so-called “mini-stroke”) or stroke, or any unexplained loss of consciousness within 1 year prior to screening 4. A brain MRI performed before treatment showed evidence of bleeding (most types of hemorrhage), diffuse white matter disease, or certain other conditions. 5. Any contraindication to having a brain MRI or PET scan 6. History of bleeding disorder 7. Use of medications with blood thinning properties, such as anti-platelet agents or anti-coagulants (except for aspirin at 325 mg daily or less) 8. Uncontrolled high blood pressure or history of unstable angina, heart attack, chronic heart failure, or clinically significant heart conduction or rhythm abnormalities
Determining level of cognitive impairment and presence of amyloid plaque	
<p>The label does not require any diagnostic tests before this drug is prescribed.</p>	<p>Before enrollment in either of the two trials, patients were required to undergo both an amyloid PET scan and detailed cognitive testing and staging.</p>

Treatment: What to expect if your healthcare provider prescribes aducanumab

- You will need monthly infusions (approximately one hour in length) for 12 to 24 months or longer. Ask your clinician where you will receive treatment. You may receive treatments in locations such as in the physician’s office or at a health care center.
- The FDA label advises that clinicians obtain MRIs before the 7th and the 12th infusions to monitor for ARIA.
- Given how little is known about whether aducanumab slows cognitive decline, you and your clinician should create a plan for closely monitoring your cognition and function over time to assess whether the treatment is slowing your cognitive decline. This plan should include discussions (at least annually) with your clinician about whether aducanumab is helping you or whether you should discontinue treatment.

Table 2: Treatment: Differences between what the FDA Approved and Study Findings

FDA Approved Use	Clinical Trials (ENGAGE, EMERGE)
Ongoing screening to assess benefit to patients	
None	Patients underwent repeated PET scans and cognitive assessments during the trials.
Screening and treatment protocol for adverse events	
<ul style="list-style-type: none"> ■ Obtain baseline MRI within one year prior to initiating treatment. ■ Obtain MRIs prior to the 7th and 12th infusions. ■ If radiographically severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates stabilization (i.e., no increase in size or number of ARIA-H). 	<ul style="list-style-type: none"> ■ To detect ARIA (see note below) throughout the aducanumab clinical program, participants had routine brain MRI scans performed at specified timepoints, with follow-up MRI scans for participants in whom ARIA was detected. Researchers used an MRI reader staffed with expert radiologists highly experienced with ARIA during the study. ■ In the clinical trial, patients with ARIA stopped taking aducanumab 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). <p>NOTE: In the studies, 30 to 40% of the participants developed “amyloid-related imaging abnormalities” (ARIA). These are changes seen in the brain using MRI scans. ARIA can be a potentially serious adverse event that causes swelling of brain tissue (edema) 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 trouble with walking. While ARIA seen on MRI scans may not cause any symptoms, some cases are severe. In the trials, if ARIA was found, treatment was discontinued until it was resolved and/or dosages were changed.</p>

Payment: What you may pay if your healthcare provider prescribes aducanumab

Biogen, aducanumab’s manufacturer, estimates that the drug’s costs will start at \$56,000 per year. Additional expenses will include facilities and staff for administering the drug by infusion, ongoing brain monitoring by clinical assessment and MRI, and any other medical care (including hospitalization) that may be necessary to deal with complications of treatment. At present, Medicare has opened a national coverage analysis (NCA), the first step in determining whether the Centers for Medicare and Medicaid Services (CMS) will cover this treatment. In August 2021, the Department of Veterans Affairs announced that it will not cover aducanumab except in patients who meet strict criteria. If you have private insurance, you should check with your insurer about coverage. Third-party insurers have not issued decisions as to what, if any, expenses they will cover.



40 FULTON STREET
18TH FLOOR
NEW YORK, NY 10038
212.308.1414 TEL
Info@healthinaging.org

The AGS Health in Aging Foundation is dedicated to improving the health, independence, and quality of life of all older people. We aim to empower older adults and caregivers to actively participate in their health care and decision-making.

DISCLAIMER: This information is not intended to diagnose health problems or to take the place of medical advice or care you receive from your physician or other healthcare provider. Always consult your healthcare provider about your medications, symptoms, and health problems. September 2021

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