LECANEMAB APPROPRIATE USE RECOMMENDATIONS

These appropriate use recommendations (AURs) are for the use of lecanemab for the treatment of early AD (ie, MCI due to AD or mild AD dementia) with confirmed brain amyloid pathology based on the clinical guidance developed by the Alzheimer's Disease and Related Disorders Therapeutics Working Group and the FDA Prescribing Information for lecanemab. This piece is part of an appropriate use toolkit independently developed by the Alzheimer's Association for HCPs who have decided to offer lecanemab for a patient meeting eligibility criteria. These AURs apply to lecanemab; other anti-amyloid monoclonal antibodies may have different management requirements. AURs specific to the monoclonal antibody being considered should be referenced.

Review this section of the toolkit to learn more about eligibility criteria for lecanemab based on the CLARITY AD trial and the appropriate use recommendations.

Patient Eligibility Criteria

ALZHEIMER'S® ASSOCIATION

Lecanemab inclusion criteria from CLARITY AD and proposed in the AUR	
Eligibility Criteria Used in the CLARITY AD Pivotal Trial of Lecanemab	**Eligibility Criteria for Lecanemab Treatment From the AUR**
Inclusion Criteria (ie, required criteria for an individual to be considered)	
Diagnosis of MCI or mild AD dementia	Clinical diagnosis of MCI or mild AD dementia[a]
Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the WMS-IV LMII	Clinical diagnosis of MCI or mild AD dementia[a]
Positive biomarker for brain amyloid pathology	Positive amyloid PET or CSF studies indicative of AD
50-90 years of age	Physician judgement used for patients outside the 50-90 year age range
MMSE score >22 at screening and baseline and <30 at screening and baseline	MMSE 22-30 or other cognitive screening instrument with a score compatible with early AD
BMI >17 and <35 at screening	Physician judgement used for patients at the extremes of BMI
If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to baseline	Patients may be on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD; patients may not be on aducanumab
Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to baseline	Patients may be on standard of care for other medical illnesses (see below for specifics regarding anticoagulation)
Have an identified study partner	Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated with lecanemab
Provide written informed consent	Patients, care partners, and appropriate family members should understand the requirements for lecanemab therapy and the potential benefit and potential harm of treatment

Please see the lecanemab exclusion criteria (ie, criteria that render an individual ineligible) on the next page.

AD, Alzheimer's disease; AUR, appropriate use recommendations; BMI, body mass index; CSF, cerebrospinal fluid; HCP, healthcare provider; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; WMS-IV LMII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

[a]MCI due to AD (intermediate likelihood) diagnostic criteria include cognitive concerns by the patient, knowledgeable informant, or the physician; objective impairment in one or more cognitive domains including memory, executive function, attention, language, and visuospatial skills; generally preserved activities of daily living; no dementia; and positive AD biomarker. Dementia diagnostic criteria include cognitive or behavioral impairment involving a minimum of 2 of the following domains: memory, executive function, visuospatial function, language, or behavior; cognitive impairment detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment; symptoms interfere with the ability to function at work or perform usual activities; decline from previous levels of functioning; and symptoms are not explained by delirium or major psychiatric disorder. MMSE score of 22-30 is used to define MCI and mild AD dementia.

Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362-377. doi:10.14283/jpad.2023.30

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Review this section of the toolkit to learn more about eligibility criteria for lecanemab based on the CLARITY AD trial and the appropriate use recommendations.

Patient Eligibility Criteria (cont'd)

ALZHEIMER'S ASSOCIATION

Lecanemab exclusion criteria from CLARITY AD and proposed in the AUR[1]	
Eligibility Criteria Used in the CLARITY AD Pivotal Trial of Lecanemab	**Eligibility Criteria for Lecanemab Treatment From the AUR**
Exclusion Criteria (ie, criteria that render an individual ineligible)	
Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD	Any medical, neurologic, or psychiatric condition that may be contributing to the cognitive impairment or any non-AD MCI or dementia
More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; multiple lacunar infarcts or stroke involving a major vascular territory; severe small vessel; or other major intracranial pathology	More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); a single macrohemorrhage >10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; more than 2 lacunar infarcts or stroke involving a major vascular territory; severe subcortical hyperintensities consistent with a Fazekas score of 3; evidence of ABRA; CAA-ri; or other major intracranial pathology that may cause cognitive impairment
Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD	MRI evidence of a non-AD dementia
History of TIA, stroke, or seizures within 12 months of screening	Recent history (within 12 months) of stroke or TIAs or any history of seizures
Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant	Mental illness (eg, psychosis) that interferes with comprehension of the requirements, potential benefit, and potential harms of treatment and are considered by the physician to render the patient unable to comply with management requirements
GDS score >8 at screening	Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. Patients with less severe depression or whose depression resolves may be treatment candidates
Any immunological disease that is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study	Any history of immunologic disease (eg, lupus erythematosus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants, immunoglobulins, or monoclonal antibodies or their derivatives
Participants with a bleeding disorder that is not adequately controlled (including a platelet count <50,000 or INR >1.5 for participants who are not on anticoagulant treatment, eg, warfarin)	Patients with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or INR >1.5 for participants who are not on an anticoagulant)
Participants who are on anticoagulant therapy should have their anticoagulant status optimized and be on a stable dose for 4 weeks before screening	Patients on anticoagulants (coumadin, dabigatran, edoxaban, rivaroxaban, apixaban, betrixaban, or heparin) should not receive lecanemab; tPA should not be administered to individuals on lecanemab
Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stably and adequately controlled, or which could affect the participant's safety or interfere with the study assessments	Unstable medical conditions that may affect or be affected by lecanemab therapy

Patients on experimental therapy were excluded from the CLARITY AD trial. Patients and their care partners should discuss with the leadership of a clinical trial of potential interest whether ongoing treatment with lecanemab is compatible with trial eligibility.[2]

ABRA, amyloid beta-related angiitis; AD, Alzheimer's disease; AUR, appropriate use recommendations; CAA-ri, cerebral amyloid angiopathy-related inflammation; GDS, Geriatric Depression Scale; HCP, healthcare provider; INR, international normalized ratio; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; TIA, transient ischemic attack; tPA, tissue plasminogen activator.

1. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362-377. doi:10.14283/jpad.2023.30 **2.** Clinicaltrials.gov. https://www.clinicaltrials.gov/study/NCT03887455#participation-criteria. Accessed January 24, 2024.

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Review this section of the toolkit to learn more about ARIA rates among *APOE4* carriers and recommendations for *APOE* testing prior to initiating lecanemab.

Apolipoprotein E (APOE) Genetic Testing

ALZHEIMER'S ASSOCIATION

APOE in humans has 3 alleles: *APOE ε3* (*APOE3*), *APOE ε2* (*APOE2*), and *APOE ε4* (*APOE4*). The *APOE4* genotype is present in ~20% to 25% of the population and increases the risk of clinical AD in a dose-dependent manner. There is a significant interaction with sex, with female *APOE4* carriers at higher risk for AD than males, particularly at younger ages. People who are *APOE4* heterozygotes possess 1 copy of the allele, while those who are homozygotes possess 2 copies of the allele. In the CLARITY AD trial, 53% of patients were heterozygous for *APOE4* and 16% were homozygous for *APOE4*.

Amyloid-related imaging abnormalities (ARIA) is a common side effect of treatment with amyloid-lowering monoclonal antibodies. Two types of ARIA can occur: ARIA-E with edema and ARIA-H with hemorrhagic changes. Risk for ARIA, symptomatic ARIA, and recurrent ARIA is higher among *APOE4* carriers (especially homozygotes). *APOE4* carriers are also at increased risk for cerebral amyloid angiopathy-related inflammation/amyloid beta-related angiitis (CAA-ri/ABRA), a risk factor for ARIA.

ARIA rates reported for the CLARITY AD trial of lecanemab

	***APOE4* Noncarrier Lecanemab (N=278)**	***APOE4* Heterozygote Lecanemab (N=479)**	***APOE4* Homozygote Lecanemab (N=141)**
ARIA-E	5.4%	10.9%	32.6%
Symptomatic ARIA-E	1.4%	1.7%	9.2%
Serious event with ARIA-E	0.7%	0.4%	2.1%
Total ARIA-H (Concurrent & Isolated)	11.9%	14.0%	39.0%

Given the increased risk for ARIA in *APOE4* carriers, *APOE* genotyping is recommended for all consenting patients being considered for lecanemab therapy before initiating treatment. The *APOE* gene produces the APOE protein, and some laboratory tests are able to determine *APOE* status by assessing the patient's proteotype. Information regarding the patient's *APOE* status will inform risk discussions and help guide safety considerations. Genotyping of a treatment candidate that reveals the patient to be an *APOE4* gene carrier has implications for all first-degree relatives, as they might share the genetic risk. Counseling regarding genotyping and its ramifications has an important role in appropriate treatment discussions.

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AD, Alzheimer's disease; *APOE*, apolipoprotein E; *APOE4*, apolipoprotein ε4 allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemorrhagic changes; HCP, healthcare provider; MCI, mild cognitive impairment.

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Review this section of the toolkit to learn more about intravenous dosing and administration of lecanemab.

Appropriate Dosing and Administration

ALZHEIMER'S ASSOCIATION

Administration

Intravenously (IV) every other week. No titration is required.

Dosing

10 mg/kg of body weight

Quantity

Vials of 500 mg/5 mL (100 mg/mL) or 200 mg/2 mL (100 mg/mL)

Preparation

Added to infusion bag containing 250 mL of 0.9% sodium chloride injection and administered through an IV line with a terminal low-protein binding 0.2 micron in-line filter

Length of Infusion

Approximately 1 hour

Post-Infusion Observation

Patients should be observed for 3 hours after first infusion with a follow-up telephone call later that day. During the call, patients should be queried about the presence of any symptoms which may indicate an infusion reaction including fever, chills, headache, rash, nausea, vomiting, abdominal discomfort, or elevated blood pressure. The post-infusion observation period may be reduced to 2 hours for the second and third infusions and to 30 minutes for subsequent infusions if no infusion reactions have occurred.

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Review this section of the toolkit to learn more about the recommended safety MRI monitoring schedule for lecanemab and when supplementation with additional MRI scans may be appropriate.

ARIA Monitoring

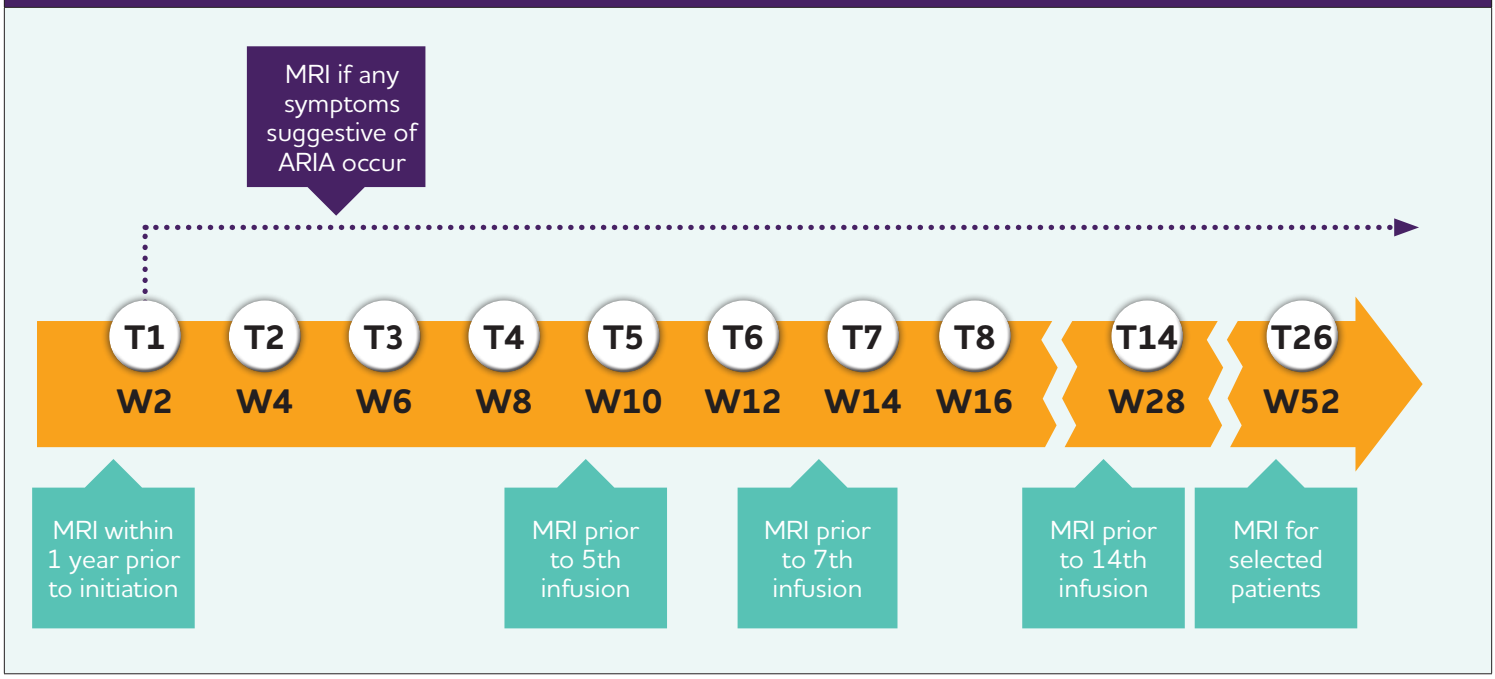
ALZHEIMER'S ASSOCIATION

Lecanemab treatment has the common side effect of amyloid-related imaging abnormalities (ARIA). Two types of ARIA occur: ARIA-E with edema and ARIA-H with hemorrhagic changes. Post-treatment monitoring recommendations aim to detect ARIA and guide management decisions that minimize the likelihood of worsening or recurrence of imaging abnormalities.

The appropriate use recommendations propose MRI scans prior to the 5th, 7th, and 14th infusions of lecanemab. Additionally, an MRI scan is recommended prior to the 26th infusion at week 52, especially in patients who are *APOE4* carriers or had evidence of ARIA (with or without symptoms) on prior scans.

In addition to scheduled safety monitoring, any symptoms suggestive of ARIA may also warrant unscheduled MRIs. Clinical considerations include the quality and intensity of the symptoms and the likelihood that they are caused by ARIA. Increased vigilance and monitoring is appropriate in *APOE4* carriers (especially homozygotes) given their increased risk for ARIA.

MRI monitoring for lecanemab



Access additional sections of the appropriate use toolkit to learn about managing adverse effects of treatment.

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AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; HCP, healthcare provider; MCI, mild cognitive impairment;
MRI, magnetic resonance imaging; T, treatment; W, week.

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Review this section of the toolkit to learn more about the radiographic grading and type of ARIA, monitoring and ongoing management, accompanying symptoms, and when lecanemab discontinuation may be appropriate.

Management of ARIA

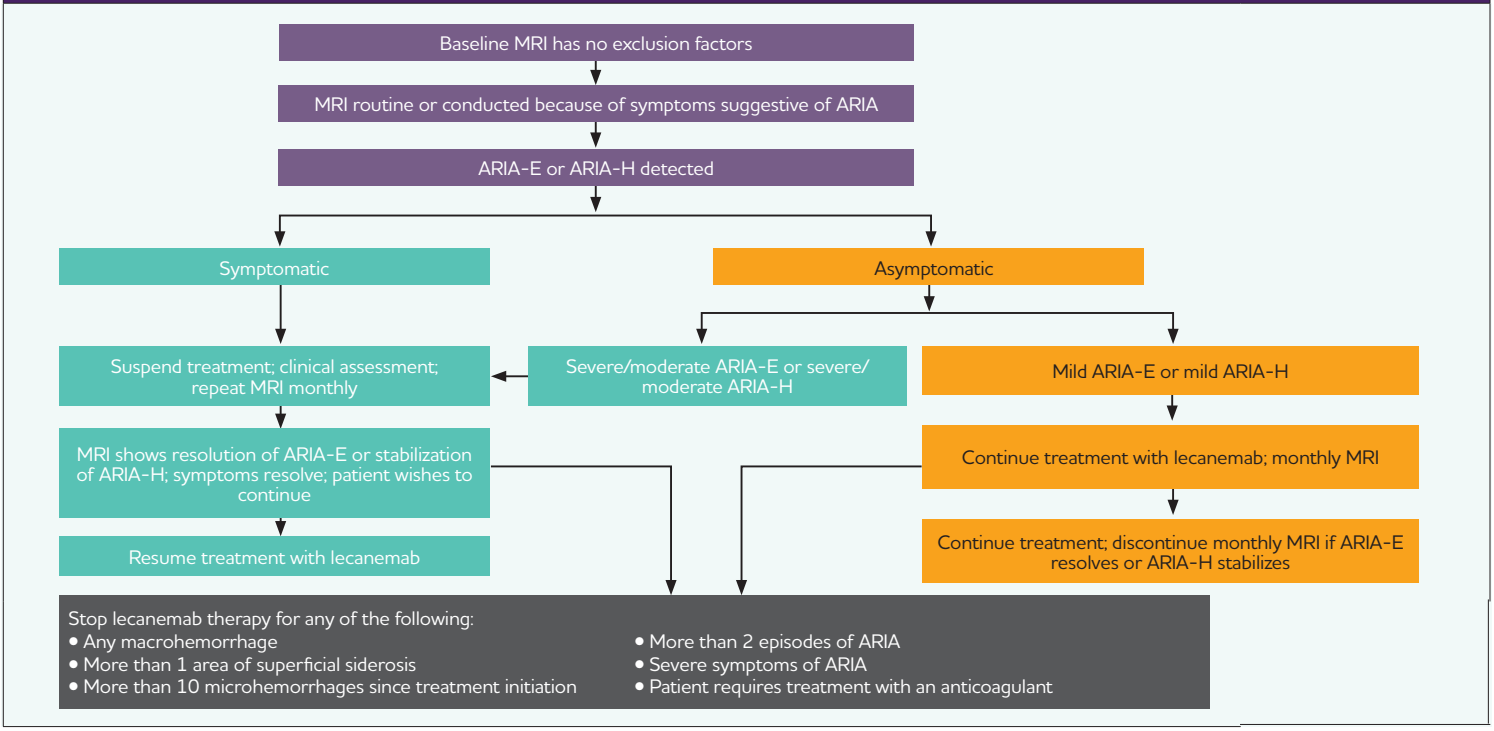
ALZHEIMER'S ASSOCIATION

A non-contrast MRI, utilizing TI FLAIR and T2*-weighted GRE or equivalent sequences (such as SWI), and DWI, preferably on a 3T magnet should be obtained. Two types of amyloid-related imaging abnormalities (ARIA) can occur: ARIA-E with edema and ARIA-H with hemorrhagic changes. In the CLARITY AD phase 3 trial of lecanemab, rates of ARIA for those on lecanemab were 12.6% for ARIA-E and 17.3% for ARIA-H vs 1.7% and 9.0%, respectively, for those on placebo.

Description of mild, moderate, and severe radiographic ARIA (from the Prescribing Information)

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in 1 location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted
ARIA-H Microhemorrhage	≤4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H Superficial Siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	>2 areas of superficial siderosis

Monitoring and management of ARIA



AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemorrhagic changes; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; GRE, gradient recalled echo; HCP, healthcare provider; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging.

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Management of ARIA (cont'd)

ALZHEIMER'S ASSOCIATION

Symptoms observed in patients who develop symptomatic ARIA

- Headache
- Confusion
- Visual changes
- Dizziness
- Nausea
- Gait difficulty
- Serious ARIA
  - Seizures
  - Status epilepticus
  - Encephalopathy
  - Stupor
  - Focal neurological deficits

Management of ARIA depending on the severity of symptoms and the severity of the radiographic ARIA-E or ARIA-H on MRI

	Symptom Description			
	No Symptoms	**Mild Symptoms**	**Moderate Symptoms**	**Severe Symptoms**
Severity of changes observed on MRI	None	Discomfort noted; no disruption of daily activity	Discomfort sufficient to reduce or affect normal daily activity	Incapacitating, with inability to work or to perform normal daily activity
ARIA-E on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing
ARIA-H on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing

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AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemorrhagic changes; HCP, healthcare provider; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

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Review this section of the toolkit to learn more about the incidence, grading, and management of infusion reactions with lecanemab.

Management of Infusion Reactions

ALZHEIMER'S ASSOCIATION

Incidence

Usually occur during the first 2 treatments and seen during the infusion or up to several hours after the infusion. In the CLARITY AD phase 3 trial of lecanemab, infusion reactions occurred in 26.4% of participants on lecanemab.

Infusion reaction symptoms

Fever, chills, headache, rash, nausea, vomiting, abdominal discomfort, and elevated blood pressure. Infusion reactions typically resolve within 24 hours and can usually be managed at home.

Grading of infusion reactions

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, NSAIDs, narcotics, IV fluids); prophylactic medication indicated for <24 hours	Prolonged recurrence of symptoms following initial improvement; hospitalization may be indicated for clinical sequelae (eg, poorly controlled hypertension)	Life-threatening consequences; urgent intervention indicated (may require pressor or ventilatory support)	Death

Managing reactions

- For mild to moderate skin hypersensitivity reactions, diphenhydramine or a topical corticosteroid cream can be used

Grade 2 Infusion Reactions

- Interrupt lecanemab
- Treat with diphenhydramine and acetaminophen every 4-6 hours until symptoms fully resolve
- 30 minutes before the next infusion after a reaction, pretreatment with oral diphenhydramine (25 mg-50 mg) and oral acetaminophen (650 mg-1000 mg) should occur
  - If this is ineffective, low-dose oral dexamethasone (0.75 mg) or oral methylprednisolone (80 mg) for management of elevated blood pressure can be given 6 hours prior to infusions
- A prophylactic regimen should be used until the patient is asymptomatic for 2-4 infusions
- If a new reaction occurs, oral diphenhydramine (25 mg-50 mg) and oral acetaminophen (650 mg-1000 mg) can be given every 4-6 hours

Grade 3 or Higher Infusion Reactions

- Discontinue lecanemab
- Significant symptoms can be treated with oral dexamethasone (0.75 mg/day for 2-3 days) or oral methylprednisolone (80 mg twice daily for 2-3 days)

AD, Alzheimer's disease; HCP, healthcare provider; IV, intravenous; MCI, mild cognitive impairment; NSAID, nonsteroidal anti-inflammatory.

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Review this section of the toolkit to learn more about when lecanemab discontinuation may be appropriate.

Stopping Lecanemab

ALZHEIMER'S ASSOCIATION

Stop lecanemab therapy for any of the following amyloid-related imaging abnormalities (ARIA)-related observations:

- Any macrohemorrhage
- More than 1 area of superficial siderosis
- More than 10 microhemorrhages since treatment initiation
- More than 2 episodes of ARIA
- Severe symptoms of ARIA
- Patient requires treatment with an anticoagulant

Stop lecanemab therapy for severe infusion reactions:

- A grade 3 or higher infusion reaction (per scoring criteria shown below)

Grading of infusion reactions

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, NSAIDs, narcotics, IV fluids); prophylactic medication indicated for <24 hours	Prolonged recurrence of symptoms following initial improvement; hospitalization may be indicated for clinical sequelae (eg, poorly controlled hypertension)	Life-threatening consequences; urgent intervention indicated (may require pressor or ventilatory support)	Death

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Review this section of the toolkit to learn more about recommended resources for the safe and effective use of lecanemab and management of serious or severe ARIA.

Clinical Workflow Considerations

ALZHEIMER'S ASSOCIATION

Resources needed by a clinician or medical center for the safe and effective use of lecanemab

- ❑ Clinician skilled in the assessment of cognition to identify individuals with MCI or mild dementia due to AD
- ❑ MRI available for baseline assessment of cerebrovascular pathology and for monitoring of amyloid-related imaging abnormalities (ARIA)
- ❑ Radiologists, neurologists, or other clinicians expert in the identification and interpretation of cerebrovascular lesions and ARIA
- ❑ Amyloid positron emission tomography or lumbar puncture capability to determine the amyloid status of treatment candidates
- ❑ Radiologists, nuclear medicine specialists, neurologists, or other specialists skilled in the interpretation of amyloid imaging or neurologist, radiologists, or other clinicians skilled in the conduct of lumbar puncture
- ❑ Apolipoprotein E genotyping resources
- ❑ Genetic expertise to counsel patients on the implications of apolipoprotein E genotyping
- ❑ Expertise in communicating with patients and care partners regarding anticipated benefits, potential harm, and requirements for administration and monitoring while on lecanemab
- ❑ Infusion settings that can be made available every 2 weeks to patients receiving therapy
- ❑ Knowledgeable staff at infusion sites capable of recognizing and managing infusion reactions
- ❑ Communication channels established between experts interpreting MRIs and clinicians treating patients with lecanemab
- ❑ Communication channels established between clinicians treating patients with lecanemab and the patient and care partner
- ❑ Availability of hospital resources for management of serious and severe ARIA including an intensive care unit
- ❑ Expertise in the management of seizures and status epilepticus for patients with serious or severe ARIA
- ❑ Protocol with standard operating procedures for management of serious and severe ARIA

Medical center resources needed to manage serious or severe ARIA

- ❑ Emergency department with resources to assess suspected or known ARIA
- ❑ MRI scanners readily available for unscheduled scanning of symptomatic patients
- ❑ Knowledgeable MRI readers proficient in detecting and interpreting ARIA
- ❑ Clinicians with experience in the management of cerebral edema or ARIA
- ❑ Hospital ward for monitoring and management
- ❑ Intensive care unit availability
- ❑ Electroencephalography available to inpatients
- ❑ Neurologist with experience in management of seizures and status epilepticus

The Alzheimer's Association Health Systems team is here to support your clinicians and systems with drug treatment readiness. Reach out to hcpservices@alz.org to be connected to a Health System Director in your area.

Please scan or click below to view the full Prescribing Information for lecanemab

Please scan or click below to view the lecanemab appropriate use recommendations publication

AD, Alzheimer's disease; ARIA, amyloid-related imaging abnormalities; HCP, healthcare provider; MCI, mild cognitive impairment;
MRI, magnetic resonance imaging.

Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis.* 2023;10(3):362-377. doi:10.14283/jpad.2023.30