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Lecanemab Appropriate Use Recommendations

Executive Summary for Health Care Professionals

ABOUT LECANEMAB

Lecanemab (Leqembi®) is an IV-administered monoclonal antibody that binds to amyloid oligomers, protofibrils and insoluble fibrils.

Approved for patients with early symptomatic Alzheimer's disease (AD), it is administered every two weeks with no dose titration (on label). A subcutaneous formulation has been announced but is not yet reflected in the published AUR. This summary will be updated once revised recommendations are available.

Slowing Alzheimer's disease (AD) progression in its early stages — mild cognitive impairment (MCI) or mild dementia — preserves intellectual and social cognition, allowing patients more time to live independently and remain engaged in daily life. The development of therapies targeting amyloid-β plaques, a core pathological feature of AD, offers a new opportunity to modify the disease course. Lecanemab (Leqembi®) is one such therapy, an anti-amyloid monoclonal antibody approved by the U.S. Food and Drug Administration (FDA) for patients with early AD and confirmed amyloid pathology.

The implementation of lecanemab in clinical practice requires a structured clinical process, from patient identification through long-term close monitoring. To provide practical guidance, this summary of the appropriate use recommendations (AUR) from the AD and Related Disorders Therapeutic Workgroup is organized into a step-by-step workflow. It is designed to help health care professionals navigate the key decisions and safety protocols required for lecanemab therapy. The **full AUR**, containing comprehensive clinical details, was published in *The Journal of Prevention of Alzheimer's Disease*.

STEP-BY-STEP WORKFLOW
For Health Care Professionals

STEP 1
Identify Potential Candidates for Lecanemab

STEP 2
Perform Required and Recommended Pre-Treatment Evaluations

STEP 3
Finalize Treatment Decision Through Shared Decision Making

STEP 4
Administer Lecanemab and Monitor Treatment

Evaluating Patients for Lecanemab Therapy

STEP 1

Identify Potential Candidates for Lecanemab

A clinician will conduct a comprehensive evaluation (including history, neurological examination, cognitive testing and initial labs/imaging) to identify patients presenting with cognitive concerns who may be candidates for lecanemab therapy. Consider evaluating patients for treatment who:

- **Present with MCI or mild dementia** consistent with AD.
- **Have symptoms reflecting gradual and progressive cognitive decline**, verified through clinical history.
- **Exhibit cognitive impairment generally aligning with an MMSE score of 20-30** or equivalent. Use the test score within clinical context and apply clinical judgment if factors like education, hearing loss, language barriers, test anxiety or apathy or a logopenic variant of the disease may affect scores.
- **Have AD as the suspected primary cause of cognitive impairment**, presenting with either typical amnestic (memory-predominant) syndrome or an established non-amnestic AD phenotype (e.g., logopenic PPA, posterior cortical atrophy).

LECANEMAB THERAPY IS NOT APPROPRIATE FOR:

- **Patients with moderate to severe dementia.**
- **Patients in the preclinical stage of the disease:** beta-amyloid positivity with no symptoms due to the amyloid.
- **Evidence of significant adverse events, or the use of certain concomitant medications** (see Step 2).

STEP 2

Perform Required and Recommended Pre-Treatment Evaluations

For potential candidates, conduct the following evaluations to confirm eligibility, identify contraindications, collect baseline information and assess risk before initiating treatment.

REQUIRED

CONFIRM AMYLOID PATHOLOGY

Treatment is appropriate only if positive amyloid status is confirmed by amyloid PET scan or CSF analysis.

Note: *Recommendations differ between using them as a step before CSF or PET confirmation, or as acceptable confirmation if the performance is equivalent to CSF tests (sensitivity and specificity of ~90% and above) and appropriate expertise and clinical context. Clinicians are using blood-based biomarkers to help ascertain the presence of amyloid pathology in patients with cognitive symptoms.**

CONDUCT BASELINE BRAIN MRI

Obtain a brain MRI (preferably 3T; however, if unavailable due to access and availability, 1.5T would be sufficient) within 12 months of treatment initiation. The MRI must ensure the absence of:

- Evidence indicating high ARIA risk, specifically >4 cerebral microbleeds or any cortical superficial siderosis (cSS).
- A single macrohemorrhage (>10 mm).
- Significant cerebrovascular disease burden (e.g., multiple or large infarcts, severe white matter disease).
- Findings suggestive of cerebral amyloid angiopathy-related inflammation (CAA-ri) or other significant structural abnormalities (e.g., tumors).

The U.S. Food and Drug Administration (FDA) **cleared the use of pTau217/β-Amyloid 1-42 plasma ratio to detect AD in patients exhibiting cognitive symptoms.*

REVIEW CONCOMITANT MEDICATIONS AND MEDICAL HISTORY

Critical Caution: Anticoagulants. Treatment should **not** be considered in e4/e4 homozygotes using anticoagulants (e.g., warfarin, apixaban, rivaroxaban) and with extreme caution in heterozygotes and non-carriers. Strong consideration should be made for alternatives to anticoagulation (i.e., a WATCHMAN device) before treatment.

Note: *Standard-dose aspirin and other antiplatelet agents (e.g., clopidogrel) when used alone are allowable.*

Treatment may not be appropriate for patients with any history of inadequately controlled seizure disorders, inadequately controlled bleeding disorders or certain immunologic disorders requiring specific therapies (i.e., IVIG) that would blunt the effect of lecanemab.

STRONGLY RECOMMENDED

ASSESS *APOE-E4* GENOTYPE STATUS

For Consideration

Due to increased risks associated with ARIA, exercise caution when considering treatment for *APOE-e4* carriers, especially homozygotes (e4/e4). All patients require diligent ARIA monitoring during lecanemab therapy.

While *APOE-e4* status does not determine eligibility, it is critical for discussing risks, monitoring and informing treatment decisions.

DETERMINE CARE PARTNER AVAILABILITY

A reliable care partner who is available and willing to participate in the patient's care and monitoring is an important factor in treatment decisions.

STEP 3

Finalize Treatment Decision Through Shared Decision Making

For confirmed eligible candidates, engage the patient and their care partner in a comprehensive discussion before making a final treatment decision. This should include:

- **Review findings** and clearly communicate results from clinical evaluation and tests, including amyloid status, key MRI findings and *APOE* genotype with associated ARIA risk implications.
- **Discuss potential benefits, risks and considerations** to ensure a thorough understanding of the potential for treatment to slow clinical decline (not cure or reverse symptoms), the individual's risk for ARIA, the potential for infusion reactions and other serious adverse events and the significant commitment required (e.g., bi-weekly infusions, surveillance MRIs, medication restrictions and prompt symptom reporting).
- **Explore alternatives** and discuss other available AD management strategies.
- **Align with patient values** and discuss how treatment may or may not align with their individual goals, values and preferences.
- **Consider obtaining informed consent/assent** and document the patient's and care partner's confirmed understanding and agreement to undertake treatment.

STEP 4

Administer Lecanemab and Monitor Treatment

For eligible patients who have collaboratively decided to move forward with treatment, initiate and manage lecanemab therapy according to AUR protocols:

- **Route and frequency:** Administered intravenously (IV) every two weeks.
- **Dose:** 10 mg/kg of body weight, no titration required.
- **Procedure:** Infuse over ~1 hour, observe post-infusion (3 hours after the first infusion, may be reduced in subsequent infusions if well-tolerated).
- **Manage infusion reactions** (see Table 10 of the full AUR for Grade definitions):
  - **Grade 1-2:** Interrupt infusion, manage symptoms (e.g., with antihistamines, acetaminophen) and consider premedication for future infusions.
  - **Grade 3+:** Consider discontinuation of lecanemab.
- **Required MRI monitoring:**
  - **Obtain safety MRIs** (FLAIR and T2*/heme sequences) prior to infusions 3*, 5, 7 and 14.
    *__Note:__ *This monitoring schedule reflects the most current guidance from the **FDA** and differs from the published AUR.*
  - **Consider an additional MRI** prior to infusion 26 (at week 52), particularly for *APOE-e4* carriers or those with prior ARIA.*
    *__Note:__ *This is an expert recommendation that extends beyond the standard FDA label.*
  - **Maintain vigilance for any clinical signs or symptoms** potentially related to ARIA or infusion reactions throughout treatment.

For more information and professional resources on anti-amyloid therapies, including systems-specific recommendations, check out the curated anti-amyloid collection on ALZPro **alz.org/Anti-Amyloid**.

Managing ARIA Risk — CRITICAL SAFETY INFORMATION

Amyloid-related imaging abnormalities (ARIA) require careful monitoring and management. Risk is significantly higher in *APOE-e4* carriers, especially homozygotes (e4/e4).

ARIA Symptoms: Can be asymptomatic (MRI finding only). Symptoms can range from mild to moderate (headache, confusion, dizziness, nausea, visual or gait changes) to severe (seizures, encephalopathy, focal deficits, death). **Any new, concerning neurological symptom requires URGENT clinical evaluation and MRI.**

Emergency Consideration: In patients on lecanemab, thrombolytics (tPA) for ischemic stroke should be avoided due to the increased risk of intracerebral hemorrhage.

ARIA Management Actions:

- **Asymptomatic mild ARIA:** Continue dosing, increase vigilance and obtain monthly MRIs until resolution or stabilization.
- **Symptomatic or moderate ARIA:** Suspend dosing, monitor clinically and obtain monthly MRIs. Consider resuming treatment only if symptoms resolve AND MRI shows ARIA-E resolution/ARIA-H stabilization AND patient and care partner provides informed agreement.
- **Severe ARIA (radiographic or symptomatic):** Permanently discontinue treatment. Requires close monitoring and potential hospitalization. Consider high-dose glucocorticoids for severe cases.

PERMANENTLY Stop Lecanemab If:

- Radiographically and clinically severe ARIA-E or ARIA-H occurs.
- Any macrohemorrhage occurs.
- A third ARIA event occurs.
- One cannot ensure radiographic stability of microhemorrhages (if they are too numerous to count).
- Patient progresses into later stage with neuropsychiatric problems or increased burden of care.
- Patient has a co-morbid medical condition that will take precedence or limit lifespan (i.e., new diagnosis or pancreatic cancer).

CONSIDER Stopping Lecanemab If:

- >1 area of superficial siderosis develops.
- >10 new microhemorrhages develop since treatment initiation.
- Patient requires anticoagulant treatment.
- A Grade 3+ infusion reaction occurs.
- Caregiver cannot be reliable due to move, illness, death or other.

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For additional information and professional resources, visit **alz.org/ALZPro.**

Reference: *Cummings J, Apostolova L, Rabinovici GD, Atri A, Aisen P, Greenberg S, Hendrix S, Selkoe D, Weiner M, Petersen RC, Salloway S. Lecanemab: Appropriate use recommendations. J Prev Alz Dis. 2023;10(3):362-377. doi:10.14283/jpad.2023.30*

This summary outlines key appropriate use recommendations designed to support health care professionals in the practical application of lecanemab for early, symptomatic Alzheimer's disease. The recommendations emphasize a structured approach encompassing patient identification, confirmation of eligibility, risk assessment (especially for ARIA via MRI and *APOE* status), informed shared decision-making and diligent monitoring. As a novel therapy, ongoing learning is expected; providers should use this summary alongside the comprehensive AUR publication and remain updated on evolving clinical data and experience to ensure the continued safe and appropriate use of lecanemab.

Understanding Appropriate Use Recommendations (AURs)

An appropriate use recommendation (AUR) provides timely, expert-informed guidance on a specific new therapy. Its development is driven by expert consensus and opinion, based on a review of available clinical trial data and regulatory information, but does not follow an extensive evidence-to-decision process. These recommendations are typically developed by independent therapeutic workgroups, and do not represent recommendations from the Alzheimer's Association or its workgroups.

About the Alzheimer's Association

The Alzheimer's Association is a worldwide voluntary health organization dedicated to Alzheimer's care, support and research. Our mission is to lead the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection and maximizing quality care and support. Our vision is a world without Alzheimer's and all other dementia®. Visit **alz.org** or call 800.272.3900.

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