

# Lecanemab (Leqembi)

## Information for healthcare professionals

*Knowing whether to use the new Alzheimer's disease drug lecanemab (trade name: Leqembi) presents a hard decision for health care professionals, families and patients. This is especially true given the absence of other satisfactory treatments for Alzheimer's disease and the media attention lecanemab has received. Here we summarize the most current evidence about lecanemab's benefits, its side effects, and its other burdens.*

### Indications for lecanemab

Lecanemab received FDA approval for the treatment of Alzheimer's disease resulting in mild cognitive impairment (MCI) or mild dementia; it has not been shown to benefit patients with moderate or severe dementia.<sup>1</sup>

The only large randomized trial of lecanemab, CLARITY-AD, used the National Institute on Aging-Alzheimer's Association Criteria to gauge the severity of cognitive impairment.<sup>2</sup> These criteria do not provide a checklist for diagnosis but instead describe combinations of cognitive changes and functional status that indicate a diagnosis of mild cognitive impairment or dementia.<sup>3,4</sup> The Clinical Dementia Rating (CDR) scale, which assigns patients a score of 0 (normal) to 3 (complete impairment) across each of 6 domains, yields total scores ranging from 0 (normal) to 18 (severe dementia). The CDR is a tool mostly for research purposes, and is not generally used in routine clinical care.<sup>5,6</sup> Instead, a combination of a brief bedside examination with other cognitive assessment tools and an inventory of activities of daily living can be used in place of the CDR to obtain a useful measure of severity of cognitive impairment.

### Benefits of lecanemab

On average, all subjects in the CLARITY-AD trial showed deterioration of cognitive function, but those given lecanemab deteriorated slightly less than controls given placebo.<sup>2</sup> A total of 1,795 patients with mild cognitive impairment or mild dementia were randomized to receive lecanemab 10 mg/kg or placebo once every 2 weeks over 18 months.

The primary outcome was change in the Clinical Dementia Rating scale Sum of Boxes (CDR-SB), which rates patients' functional capacity from 0 to 3 across six domains including memory, orientation, judgement, community affairs, home and hobbies, and personal care. Higher scores indicate worsening dementia severity: a score of <0.5-4.0 indicates mild cognitive impairment while scores from 4.5 to 9 indicate mild dementia.<sup>7</sup> In the CLARITY-AD trial, the mean baseline CDR-SB score was 3.2 in patients receiving lecanemab or placebo. At 18 months, those randomized to receive lecanemab had an increase in their CDR-SB score (i.e., worsening dementia) of approximately 1.2 points, whereas those randomized to placebo had an increase of approximately 1.7 points. This represents a difference between groups of 0.45 points (95%CI -0.67 to -0.23, p<0.001). Some have characterized this as a meaningful slowing of decline, while others have questioned whether it will even be noticeable by patients or families.

In addition to this primary result, several secondary endpoints in CLARITY-AD also favored lecanemab. These included greater reductions in brain amyloid levels as well as slower worsening of cognitive decline as measured by scores on other scales such as the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog14), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Cooperative Study-Activities of Daily Living for Mild Cognitive Impairment (ADCS-MCI-ADL).

While the consistency of the primary and secondary endpoints in CLARITY-AD suggests that lecanemab is statistically significantly different from placebo, there are important caveats to consider:

- On average, cognitive functioning did not improve in patients taking lecanemab.
- In the 18 month trial duration, cognitive status was stable in most patients (76% of patients who received lecanemab versus 67% of patients who received placebo).
- On the 18-point CDR-SB used, it is not clear whether the 0.45 point smaller decline in patients given lecanemab compared to placebo will be clinically meaningful in terms of daily functioning.
- The trial was limited to people with MCI or mild dementia due to Alzheimer's disease; it didn't provide any evidence on whether the drug would be useful in patients with moderate or severe disease.
- In post hoc subgroup analyses, benefits for lecanemab were negligible for women, for those with the gene variant apolipoprotein E  $\epsilon$ 4 (ApoE  $\epsilon$ 4 homozygotes) and for people under 65.

## Side effects of lecanemab

In CLARITY-AD, 45% of patients given lecanemab had an adverse event, compared to 22% of patients randomized to placebo. Some of these were considered serious; 14% of patients who received lecanemab had a serious adverse event compared with 11% who received placebo.

The most common adverse event was infusion-related reactions, which occurred in 26% of patients randomized to lecanemab and 7% randomized to placebo. In addition, amyloid-related imaging abnormalities (ARIA) were twice as common in patients receiving lecanemab (14.0% vs. 7.7%).<sup>2</sup> ARIA are abnormalities seen on MRI that reflect brain effusion or hemorrhage. Among Phase 3 trial subjects taking an anticoagulant alone or with an antiplatelet medication, 2.4% of patients randomized to lecanemab had a cerebral hemorrhage evident on MRI compared to none who received placebo.<sup>8</sup> For this reason, the manufacturer suggests "exercising caution" when using anticoagulation or thrombolytic agents (e.g., tPA) with lecanemab. ARIA was also much more common in patients homozygous for ApoE  $\epsilon$ 4. Brain bleeding or hemorrhage occurred in 45% of such patients receiving the drug compared with 22% receiving placebo. For ApoE  $\epsilon$ 4 heterozygotes, the risk of ARIA was only slightly increased. The FDA and manufacturer suggest testing for ApoE  $\epsilon$ 4 status prior to initiation of treatment.



Over time, patients in randomized trials of amyloid-attacking drugs such as lecanemab have been found on average to lose brain volume, compared to subjects given comparison treatments. The clinical implications of this finding are not well understood.<sup>9</sup>

# Other considerations

## Need for intravenous infusion

Lecanemab must be given every two weeks through an intravenous infusion over about an hour. Patients must be able to access an infusion center and spend about 2 hours per visit every other week for at least 18 months. It is not yet known how long lecanemab should be continued beyond the 18 months studied.<sup>10</sup>

## Required imaging studies

Lecanemab should be given only to people with documented elevated brain amyloid levels. Therefore, before treatment is started patients must undergo either a lumbar puncture or PET scan. Patients must also undergo a baseline MRI brain scan. A clinical diagnosis of MCI or dementia is an unreliable marker of elevated brain amyloid.

After a course of lecanemab is started, additional MRI scans are required during treatment – about once every 3 months for the first year, and more often for patients who develop worrisome symptoms.

## Costs

The manufacturer of lecanemab has set a list price of about \$26,500 per patient for each year of treatment; that does not include the additional costs of doctor visits, tests, and infusion charges, which have been estimated at about \$7,300 more per year – making for a total of \$33,800 or more per year.<sup>11</sup> Medicare will pay 80% of the cost of the drug for people with Part B coverage - with the rest of the bill potentially payable by the patient. Many patients in Medicare have supplemental (Medigap) coverage that can help pay that amount, or they may be enrolled in a Medicare Advantage or retiree health insurance plan that may do so. However, one estimate found that for some Medicare patients, their share of the total bill could be as high as \$6,600 per year.<sup>10</sup>

## Ongoing evaluation

Medicare recognizes there are still uncertainties around the risks and benefits of anti-amyloid monoclonal antibodies in Alzheimer's Disease.<sup>12</sup> CMS therefore requires that all patients prescribed lecanemab must be enrolled in a nationwide registry to gather more information on its effects and risks. These registries will capture relatively limited amounts of information, and it is not clear how useful they will be for informing practice.

## Summary

There is still no medication that stops the progression of Alzheimer's disease. However, lecanemab does slow this progression somewhat compared with placebo, which will make lecanemab appealing for many patients. Unfortunately, its modest benefits may or may not be noticeable to patients and families, and its use comes with a small but definite risk of potentially severe side effects. The burden of getting to an infusion center every two weeks will be challenging for many patients, and use of lecanemab will require ongoing imaging studies. Patients and families should be informed of these issues to help guide their decisionmaking. Lecanemab might still be a reasonable choice for some patients and families willing to deal with its potential downsides in their quest to try and slow the pace of this cruel disease. But for many others, the drug's limited benefits, worrisome risks, and substantial toll may not be a tradeoff worth making.



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## References

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More information on Alzheimer's disease and caring for older patients with cognitive impairment is at: [AlosaHealth.org/dementia/](https://AlosaHealth.org/dementia/)

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**These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.**

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