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Safety Concerns Remain Ahead Of FDA Ad Comm On Donanemab

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FDA is widely expected to approve Eli Lilly's Alzheimer's drug donanemab following a meeting of its Peripheral and Central Nervous System Drug Advisory Committee meeting Monday (June 10). But some scientists are warning that Lilly's trial data of the drug is incomplete, and FDA would be relying on the company to make safety and efficacy decisions on the drug.

In a briefing document posted online Thursday (June 6), FDA said brain bleeding, infusion-related reactions and hypersensitivity remain significant safety concerns but also offers a positive outlook of the drug.

In Lilly's clinical trial, 37% of the participants who received donanemab experienced side effects associated brain bleeding and swelling, known as amyloid-related imaging abnormalities (ARIA), and three patients died as a result of these complications. Concerns about ARIA were part of the reason FDA declined to grant accelerated approval to donanemab last year.

Lilly's data show the drug is able to slow progression of Alzheimer's, especially for patients in earlier stages of the disease. The company is asking FDA to approve it without restrictions for patients with mild dementia or early symptomatic Alzheimer's disease.

CMS has imposed class-wide national coverage determinations (NCDs) for Alzheimer's drugs in the same class as donanemab, monoclonal antibodies that counter amyloid beta plaque on the brain to treat Alzheimer's disease. The agency declined to cover anti-amyloid drugs that receive accelerated approval for most beneficiaries and requires patients receiving Biogen and Eisai's anti-amyloid, Leqembi, to participate in a registry even after the drug received traditional approval.

The NCD includes coverage with evidence development (CED) requirements that ask drug makers to answer three key questions to CMS: whether the drug improves health outcomes in broad community practice, whether drug risks such as brain hemorrhage vary based on patient characteristics, and how the risk and benefits of the drug change over time.

If donanemab is approved, FDA says it would add a black box warning, the agency's strongest caution, to its label, noting that the class of amyloid-targeting medicines to which it belongs is associated with brain swelling or bleeding, hypersensitivity and infusion-related reactions.

The labeling would provide recommendations for magnetic resonance imaging (MRI) monitoring to document the timing and symptoms of ARIA events in clinical studies. For post market surveillance of donanemab, clinicians would need to report any deaths resulting from brain swelling and bleeding that is greater than one centimeter in size as well as seizures and fatality.

Some scientists say FDA's history with anti-amyloid drugs raises questions on whether the agency will listen to the experts on the Monday advisory panel.

Eric Widera, clinician and educator in the Division of Geriatrics at University of California San Francisco, told *Inside Health Policy* that FDA's decision to hold an advisory panel on donanemab is a "good move," but pointed out that the agency overruled the committee's recommendation in the case of Biogen's Alzheimer's drug Aduhelm.

"I think what happens next is going to be the most important part," Widera said. "How are they mitigating conflicts

of interests? And does the FDA listen to them if it's not what they want to hear?"

The scientific questions raised about the efficacy of donanemab are the same as they were for Adulhem and Leqembi, according to Widera.

"It goes to show you how little we know about all of this, and this rush to push medications like aducanumab (Adulhem) and lecanemab (Lequembi) when there are so many questions about them," Widera said.

Widera also points out that there is not enough information on how these class of Alzheimer's drugs works beyond an 18-month trial period, including for donanemab.

"Dementia is a disease that progresses over many years, not just 18 months," he said.

FDA issued an updated guidance in March on Alzheimer's disease drug development that includes a new section emphasizing reduction in amyloid beta levels as a surrogate endpoint that's predictive of clinical benefit, signaling its ongoing endorsement of amyloid reduction as a proxy for slowing disease progression.

FDA's controversial approval of Aduhelm despite advisers' dissent resulted in panel resignations and a troubled commercial launch. The company has since pulled the drug from the market.

Safety concerns

The most common side effects of donanemab are ARIA-E, which indicates swelling and was found in 24% of patients on the drug, and ARIA-H, which indicates bleeding and was observed in 31% of patients.

These rates are about twice as high as those seen in Eisai and Biogen's study of Leqembi. Serious cases, which might require hospitalization, occurred in 2% of patients treated in Lilly's trial.

Data initially suggested that deaths may have been more common among those who received donanemab than those in a control group, a concern for the agency. FDA document notes that 17 patients on donanemab died compared to 10 who received a placebo.

"An increased risk of ARIA-E and ARIA-H has been observed in donanemab-treated patients with pretreatment microhemorrhage and/or superficial siderosis," FDA's document says.

Further examination of the mortality rates revealed that nearly a quarter of study participants dropped out before the study concluded, leaving Lilly uncertain about their survival status.

FDA also notes in the document that patients who received donanemab experienced slightly more brain shrinkage compared to those who received a placebo. While brain volume loss is anticipated in Alzheimer's patients, the agency indicates that the significance of this finding remains unclear and emphasizes the importance of longer-term studies involving more patients.

In a viewpoint article published in *JAMA Network* on May 6, two scientists note the trial studies of donanemab reported treatment-related loss in brain volume but did not address whether these changes were related to lesser cognitive and functional outcomes.

"Although published results from trials of aducanumab, lecanemab, and donanemab have all reported treatment-related loss in brain volume and/or expansion in ventricular volume, they have not addressed whether these changes were related to poorer cognitive and functional outcomes," they wrote.

The viewpoint article also says its crucial companies provide access to post-market surveillance data without delay to better assess risk-benefit discussions that clinicians would have with their patients.

"Information about longer-term cognitive and functional outcomes from open-label ex-tension treatment periods and from post-trial surveillance should be made available without undue delay to better inform the risk-benefit discussions that prescribers will have with their patients," the scientists wrote.

Efficacy concerns

According to FDA's document, Lilly altered the primary endpoint of its Phase 3 trial from the conventional CDR-SB,

a standard measure of cognition and function, to its proprietary metric called iADRS.

Lilly has asserted that this new assessment, which merges two other cognitive tests, offers a more accurate reflection of patient progress. FDA did not agree with this method and advised Lilly against using iADRS as the primary endpoint. Lilly proceeded with iADRS but retained the standard scale as a secondary measure.

Last summer, Lilly revealed that donanemab slowed the progression of the disease by 22% according to Lilly's scale and by 29% according to the standard scale. This claim is based on a subset of the study participants -- those with low-to-medium levels of tau proteins in their brains. FDA notes in the document that the potential benefits might be more restricted in patients with high tau levels.

Leaders of the American Geriatrics Society (AGS) wrote a letter Friday (June 7) to FDA's advisory panel to ask whether ARIA is associated with worsening of memory and functional abilities in the long-run as there is currently no data to help clinicians decide whether they should continue prescribing these drugs with ARIA-related symptoms.

"We understand the heavy toll of Alzheimer's disease on patients, caregivers, and their families and are supportive of the FDA approving safe and effective new treatments," they wrote. "However, we believe there is still a lot we do not know about the potential benefits and harms of drugs in the anti-amyloid class."

Lilly's evidence claim

Lilly's scientists gathered data from various studies the company has done in Phase 3 trials and answered the three questions CMS poses in its NCD in a paper published in February in *The Journal of The Alzheimer's Association*.

The scientists found that donanemab helped people in advanced stages of Alzheimer's disease but treating people in earlier stages slowed down the disease progression the most.

In a study with 1,700 patients in the early stages of the disease, the drug slowed Alzheimer's progression by 35% compared to a placebo.

Lilly claims that evidence from studies like its TRAILBLAZER clinical trial supports not restricting the use and coverage of donanemab.

"Robust evidence from the TRAILBLAZER-ALZ clinical development program supports that donanemab should not be restricted based on treating clinician or treatment setting," the paper says. "90% of TRAILBLAZER-ALZ 2 study and enrollment was from community-based clinics or nonacademic centers, reflecting the treatment setting expected for most patients in a real-world setting."

Knowledge gaps

Despite Lilly's evidence claim, scientists and industry leaders say in Lilly's TRAILBLAZER-ALZ 2 study on donanemab, people of color made up less than 10% of the participants.

"Considering the racial and ethnic disparities in the prevalence of AD (Alzheimer's drug) and other dementias among the subpopulations and increasing diversity among older people, it is important to determine whether age, gender, and racial and ethnic representation in trials is sufficient to support generalizability," AGS president Mark Supiano and AGS CEO Nancy Lundebjerg wrote in the Friday letter.

Supiano and Lundebjerg say FDA's advisory committee should ask Lilly to make the subgroup analysis publicly available and ask FDA to issue guidance for Lilly to outline subgroups not represented in the trial and collect post-market data of these subgroups. They also ask FDA to include information about the participants excluded from participation in the donanemab clinical trial.

"For donanemab and all drugs in this class, more information is needed about the longer-term cognitive and functional outcomes to inform discussion of the potential benefits and harms that prescribing clinicians will have with their patients," Supiano and Lundebjerg wrote.

In the letter, they ask FDA to consider putting donanemab under a Risk Evaluation and Mitigation (REM) strategy to ensure that there is extra effort on monitoring, preventing and managing serious risks and side effects of the

drug.

Jayne Hornung, chief clinical officer at the market access intelligence firm MMIT, said she expects FDA to approve donanemab, which she sees as having a slightly better safety and efficacy profile than Leqembi, though the product is likely to carry the same safety warnings. "I don't see a reason for them to say no," she said.

Hornung anticipated that CMS will cover donanemab under the same conditions the agency has set for Leqembi, including requiring participation in a registry. She said the drug will offer more hope to Alzheimer's patients in slowing the progression of the disease, but also represents only the beginning of Alzheimer's drug development.

"We've been studying for a long time, but we've just started finding products that will slow the progression," she said. "The industry is going to find more targets, just like we treat cancer patients and their different targets, because cancer develops for all different reasons. The same thing, I think, is going to happen with Alzheimer's."

Hornung said a "moonshot" for Alzheimer's disease, similar to what the Biden administration is striving to do for cancer cures, would help drug developers put more resources toward understanding and working on treatments for the disease. -- *Maaisha Osman* (mosman@iwpnews.com), *Jessica Karins* (jkarins@iwpnews.com)

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