

March 13, 2023
Eisai Co., Ltd.

**U.S. VETERANS' HEALTH ADMINISTRATION (VHA) PROVIDES COVERAGE OF LEQEMBI™
(LECANEMAB-IRMB) TWO MONTHS AFTER LEQEMBI'S FDA ACCELERATED APPROVAL FOR
VETERANS LIVING WITH EARLY STAGES OF ALZHEIMER'S DISEASE**

*EISAI IS PROUD TO SUPPORT U.S. VETERANS LIVING WITH EARLY STAGES OF ALZHEIMER'S
DISEASE AND WILL CONTINUE TO TRANSPARENTLY SHARE OUR HIGH-QUALITY DATA WITH
THE VHA*

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the U.S. Veterans' Health Administration (VHA) is providing coverage of LEQEMBI™ (lecanemab-irmb) to veterans living with early stages of Alzheimer's disease (AD). VHA healthcare professionals meeting the criteria set forth by the VHA can prescribe LEQEMBI to veterans who fit the VHA's criteria and the U.S. Food and Drug Administration's (FDA) current label. The VHA's careful consideration and timely action to make LEQEMBI available approximately two months after the FDA approved LEQEMBI under the accelerated approval pathway shows its continued commitment to veterans living with AD.

If approved under the traditional pathway, the FDA will update the label for LEQEMBI, which will include new data that has been evaluated by the FDA. Eisai looks forward to sharing additional high-quality data as it becomes available and to continuing discussions with the VHA as the company prepares for the FDA's potential conversion of LEQEMBI's accelerated approval to a traditional approval. Eisai is proud of and humbled by the opportunity to support U.S. veterans as we strive to fulfill our human health care (*hhc*) mission.

LEQEMBI is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (protofibrils*) and insoluble forms of amyloid beta (Aβ). LEQEMBI was approved in the U.S. under the Accelerated approval Pathway for the treatment of AD on January 6, 2023, and was launched in the U.S. on January 18, 2023. Treatment with LEQEMBI should only be initiated in patients with mild cognitive impairment or mild dementia stage of disease and confirmed presence of Aβ pathology.

The Accelerated approval was based on Phase 2 data that demonstrated that LEQEMBI reduced the accumulation of Aβ plaque in the brain, a defining feature of AD, and its continued approval may be contingent upon verification of LEQEMBI's clinical benefit in a confirmatory trial. The FDA has determined that the results of Clarity AD will serve as the confirmatory study to verify the clinical benefit of LEQEMBI.

On the same day that LEQEMBI received its Accelerated approval, Eisai submitted the supplemental Biologics License Application (sBLA) to the FDA for approval under the Traditional pathway. The sBLA was accepted by the FDA on March 3, 2023 and granted Priority Review with a Prescription Drug User Fee Act (PDUFA) date of July 6, 2023. The sBLA is based on the findings from Eisai's recently

published large, global confirmatory Phase 3 clinical trial, Clarity AD. LEQEMBI met the primary endpoint and all key secondary endpoints with highly statistically significant results. In November 2022, results of the Clarity AD study were presented at the [Clinical Trials on Alzheimer's Disease \(CTAD\) conference](#) and simultaneously published in the peer-reviewed medical journal, [The New England Journal of Medicine](#).

Eisai serves as the lead of LEQEMBI development and regulatory submissions globally with both Eisai and Biogen co-commercializing and co-promoting the product and Eisai having final decision-making authority.

* Protofibrils are large A β aggregated soluble species of 75-500 Kd.¹

To learn more, visit <http://www.legembi.com/>.

INDICATION, DOSAGE AND ADMINISTRATION, AND IMPORTANT SAFETY INFORMATION IN THE U.S.

INDICATION

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Amyloid Related Imaging Abnormalities

LEQEMBI can cause amyloid related imaging abnormalities-edema (ARIA-E) and -hemosiderin deposition (ARIA-H). ARIA-E can be observed on MRI as brain edema or sulcal effusions, and ARIA-H as microhemorrhage and superficial siderosis. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. Reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time.

ARIA Monitoring and Dose Management Guidelines

Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment with LEQEMBI. Obtain an MRI prior to the 5th, 7th, and 14th infusions.

Recommendations for dosing in patients with ARIA-E and ARIA-H depend on clinical symptoms and radiographic severity. Depending on ARIA severity, use clinical judgment in considering whether to continue dosing, temporarily discontinue treatment, or permanently discontinue LEQEMBI.

Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be

performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

There is no experience in patients who continued dosing through symptomatic ARIA-E or through asymptomatic, but radiographically severe, ARIA-E. There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E.

Incidence of ARIA

In Study 1 (Study 201), symptomatic ARIA occurred in 3% (5/161) of LEQEMBI-treated patients. Clinical symptoms associated with ARIA resolved in 80% of patients during the period of observation.

Including asymptomatic cases, ARIA was observed in LEQEMBI: 12% (20/161); placebo: 5% (13/245). ARIA-E was observed in LEQEMBI: 10% (16/161); placebo: 1% (2/245). ARIA-H was observed in LEQEMBI: 6% (10/161); placebo: 5% (12/245). There was no increase in isolated ARIA-H for LEQEMBI compared to placebo.

Intracerebral hemorrhage >1 cm in diameter was reported after one treatment in LEQEMBI: 1 patient; placebo: zero patients. Events of intracerebral hemorrhage, including fatal events, in patients taking LEQEMBI have also been reported in other studies.

Apolipoprotein E ϵ 4 (ApoE ϵ 4) Carrier Status and Risk of ARIA

In Study 1, 6% (10/161) of patients in the LEQEMBI group were ApoE ϵ 4 homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers.

The incidence of ARIA was higher in ApoE ϵ 4 homozygotes than in heterozygotes and noncarriers among patients treated with LEQEMBI. Of the 5 LEQEMBI-treated patients who had symptomatic ARIA, 4 were ApoE ϵ 4 homozygotes, 2 of whom experienced severe symptoms. An increased incidence of symptomatic and overall ARIA in ApoE ϵ 4 homozygotes compared to heterozygotes and noncarriers in LEQEMBI-treated patients has been reported in other studies.

The recommendations on management of ARIA do not differ between ApoE ϵ 4 carriers and noncarriers. Consider testing for ApoE ϵ 4 status to inform the risk of developing ARIA when deciding to initiate treatment with LEQEMBI.

Radiographic Findings

The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients treated with LEQEMBI was mild in 4% (7/161) of patients, moderate in 4% (7/161) of patients, and severe in 1% (2/161) of patients. Resolution on MRI occurred in 62% of ARIA-E patients by 12 weeks, 81% by 21 weeks, and 94% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with LEQEMBI was mild in 4% (7/161) of patients and severe in 1% (2/161) of patients; 1 of the 10 patients with ARIA-H had mild superficial siderosis.

Concomitant Antithrombotic Medication and Other Risk Factors for Intracerebral Hemorrhage

Patients were excluded from enrollment in Study 1 for baseline use of anticoagulant medications. Antiplatelet medications such as aspirin and clopidogrel were allowed. If anticoagulant medication was used because of intercurrent medical events that required treatment for ≤ 4 weeks, treatment with

LEQEMBI was to be temporarily suspended.

Most exposures to antithrombotic medications were to aspirin; few patients were exposed to other antiplatelet drugs or anticoagulants, limiting any meaningful conclusions about the risk of ARIA or intracerebral hemorrhage in patients taking other antiplatelet drugs or anticoagulants. Because intracerebral hemorrhages >1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

Patients were excluded from enrollment in Study 1 for the following risk factors for intracerebral hemorrhage: prior cerebral hemorrhage >1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, and severe small vessel or white matter disease. Caution should be exercised when considering the use of LEQEMBI in patients with these risk factors.

Infusion-Related Reactions

Infusion-related reactions were observed in LEQEMBI: 20% (32/161); placebo: 3% (8/245); and the majority of cases in LEQEMBI-treated patients (88%, 28/32) occurred with the first infusion. All infusion-related reactions were mild (56%) or moderate (44%) in severity. Infusion-related reactions resulted in discontinuations in 2% (4/161) of patients treated with LEQEMBI. Symptoms of infusion-related reactions included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.

After the first infusion, 38% of LEQEMBI-treated patients had transient decreased lymphocyte counts to $<0.9 \times 10^9/L$ compared to 2% on placebo, and 22% of LEQEMBI-treated patients had transient increased neutrophil counts to $>7.9 \times 10^9/L$ compared to 1% on placebo.

In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids prior to future infusions may be considered.

ADVERSE REACTIONS

In Study 1, 15% of LEQEMBI-treated patients, compared to 6% of placebo-treated patients, stopped study treatment because of an adverse reaction. The most common adverse reaction leading to discontinuation of LEQEMBI was infusion-related reactions that led to discontinuation in 2% (4/161) of patients treated with LEQEMBI compared to 1% (2/245) of patients on placebo.

The most common adverse reactions reported in $\geq 5\%$ of patients treated with LEQEMBI (N=161) and $\geq 2\%$ higher than placebo (N=245) in Study 1 were infusion-related reactions (LEQEMBI: 20%; placebo: 3%), headache (LEQEMBI: 14%; placebo: 10%), ARIA-E (LEQEMBI: 10%; placebo: 1%), cough (LEQEMBI: 9%; placebo: 5%), and diarrhea (LEQEMBI: 8%; placebo: 5%).

Please see full [Prescribing Information](#) in the U. S.

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[Notes to editors]

About LEQEMBI™ (lecanemab-irmb)

LEQEMBI™ (lecanemab-irmb) is the result of a strategic research alliance between Eisai and BioArctic. LEQEMBI is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (protofibril) and insoluble forms of amyloid-beta (Aβ). In the U.S., LEQEMBI was granted accelerated approval by the U.S. Food and Drug Administration (FDA) on January 6, 2023. LEQEMBI is indicated for the treatment of Alzheimer's disease (AD) in the U.S. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in Aβ plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

In the U.S., Eisai submitted a supplemental Biologics License Application (sBLA) to the FDA for approval under the traditional pathway on January 6, 2023. On March 3, 2023, the FDA accepted Eisai's sBLA based on the Clarity AD clinical data, and the LEQEMBI application has been granted Priority Review, with a Prescription Drug User Fee Act (PDUFA) action date of July 6, 2023. The Clarity AD study of lecanemab met its primary endpoint and all key secondary endpoints with highly statistically significant results. Eisai submitted an application for manufacturing and marketing approval to the Pharmaceuticals and Medical Devices Agency (PMDA) on January 16, 2023, in Japan. The Priority Review was granted by the Ministry of Health, Labour and Welfare (MHLW) on January 26, 2023. Eisai utilized the prior assessment consultation system of PMDA, with the aim of shortening the review period for lecanemab. In Europe, Eisai submitted a marketing authorization application (MAA) to the European Medicines Agency (EMA) on January 9, 2023, and accepted on January 26, 2023. In China, Eisai initiated submission of data for a BLA to the National Medical Products Administration (NMPA) of China in December 2022, and the Priority Review was granted on February 27, 2023.

Eisai has completed lecanemab subcutaneous bioavailability study, and subcutaneous dosing is currently being evaluated in the Clarity AD OLE.

Since July 2020, Eisai's Phase 3 clinical study (AHEAD 3-45) for individuals with preclinical AD, meaning they are clinically normal and have intermediate or elevated levels of amyloid in their brains, is ongoing. AHEAD 3-45 is conducted as a public-private partnership between the Alzheimer's Clinical Trial Consortium (ACTC) that provides the infrastructure for academic clinical trials in AD and related dementias in the U.S., funded by the National Institute on Aging, part of the National Institutes of Health,

Eisai and Biogen. The Tau NexGen clinical study for Dominantly Inherited AD (DIAD), that is conducted by Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), led by Washington University School of Medicine in St. Louis, has been ongoing since January 2022.

About the Collaboration between Eisai and Biogen for AD

Eisai and Biogen have been collaborating on the joint development and commercialization of AD treatments since 2014. Eisai serves as the lead of lecanemab development and regulatory submissions globally with both companies co-commercializing and co-promoting the product and Eisai having final decision-making authority.

About the Collaboration between Eisai and BioArctic for AD

Since 2005, Eisai and BioArctic have had a long-term collaboration regarding the development and commercialization of AD treatments. Eisai obtained the global rights to study, develop, manufacture and market LEQEMBI for the treatment of AD pursuant to an agreement with BioArctic in December 2007. The development and commercialization agreement on the antibody LEQEMBI back-up was signed in May 2015.

References

¹ Söderberg, L., Johannesson, M., Nygren, P. et al. Lecanemab, Aducanumab, and Gantenerumab — Binding Profiles to Different Forms of Amyloid-Beta Might Explain Efficacy and Side Effects in Clinical Trials for Alzheimer's Disease. *Neurotherapeutics* (2022). <https://doi.org/10.1007/s13311-022-01308-6>. Accessed February 9, 2023

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