FDA Grants Traditional Approval for LEQEMBI® (lecanemab-irmb) for the Treatment of Alzheimer's Disease

July 6, 2023

The first and only approved treatment shown to reduce the rate of disease progression and to slow cognitive and functional decline in adults with Alzheimer's disease

The Centers for Medicare & Medicaid Services (CMS) announced broader Medicare coverage of LEQEMBI

TOKYO and CAMBRIDGE, Mass., July 06, 2023 (GLOBE NEWSWIRE) -- Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq: BIIB, Corporate headquarters: Cambridge, Massachusetts, CEO: Christopher A. Viehbacher, "Biogen") announced today that the U.S. Food and Drug Administration (FDA) has approved the supplemental Biologics License Application (sBLA) supporting the traditional approval of LEQEMBI® (lecanemab-irmb) 100 mg/mL injection for intravenous use, making LEQEMBI the first and only approved treatment shown to reduce the rate of disease progression and to slow cognitive and functional decline in adults with Alzheimer's disease (AD). LEQEMBI demonstrated clinically meaningful slowing of cognitive and functional decline in a patient group generalizable to U.S. Medicare beneficiaries, which included a mix of racial and ethnic groups, patients with common comorbid conditions, concomitant medications and patients with mild cognitive impairment (MCI) due to AD or mild AD. Treatment with LEQEMBI should be initiated in patients with MCI or mild dementia stage of disease, (collectively referred to as early AD) the population in which treatment was initiated in clinical trials.

LEQEMBI's traditional approval is based on Phase 3 data from Eisai's large, global Clarity AD clinical trial, in which LEQEMBI met its primary endpoint and all key secondary endpoints with statistically significant results and confirmed the clinical benefit of LEQEMBI. The primary endpoint was the global cognitive and functional scale, Clinical Dementia Rating Sum of Boxes (CDR-SB). LEQEMBI treatment reduced clinical decline on CDR-SB by 27% at 18 months compared to placebo. Additionally, the secondary endpoint of AD Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL), as measured by people caring for patients with AD, noted a statistically significant benefit of 37%. This measures the ability of patients to function independently, including being able to dress, feed themselves and participate in community activities. Full results of the Clarity AD study were presented at the Clinical Trials on Alzheimer's Disease (CTAD) 2022 conference and simultaneously published in the peer-reviewed medical journal *The New England Journal of Medicine* on November 29, 2022.

Importantly, following FDA's traditional approval of LEQEMBI, CMS confirmed that broader coverage of LEQEMBI is now available and released more details on the registry, including the easy-to-use data submission process. The CMS-facilitated registry is now available for healthcare professionals to submit required patient data to CMS. Eisai is pleased that Medicare will cover this important therapy for appropriate patients. This will facilitate reimbursement for and access to LEQEMBI across a broad range of healthcare settings in the United States.

"Today, the FDA approved LEQEMBI under the traditional approval pathway, making LEQEMBI the first and only approved anti-amyloid Alzheimer's disease treatment shown to reduce the rate of disease progression and to slow cognitive impairment in the early and mild dementia stages of the disease. As a research and development-focused company based on our *hhc (human health care)* concept, we are proud that the results of Eisai's AD research over the past 40 years have been recognized and delivered to people living with this disease in the United States," said Haruo Naito, Chief Executive Officer at Eisai. "Alzheimer's disease is a progressive, fatal disease that greatly impacts not only the people living with it, but also their loved ones, care partners and society. We continue to work to create broad and simple access to LEQEMBI for patients and to support diagnosis and treatment at the early stage of the disease. Eisai will diligently work to educate physicians on the safe and appropriate use of LEQEMBI to maximize its benefit to people living with early AD and their families."

"Today marks a breakthrough in the treatment of Alzheimer's disease, and we are proud to be at the forefront of ushering in a new era of advances for a disease that was previously considered untreatable. We would like to express our sincere appreciation to those who have worked tirelessly to find a treatment for this unrelenting disease, without whom this progress would not be possible," said Christopher A. Viehbacher, President and Chief Executive Officer of Biogen. "Our focus is now on the path forward, working alongside Eisai with the goal of making LEQEMBI accessible to eligible patients as soon as possible."

LEQEMBI is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (protofibril*) and insoluble forms of amyloid beta (Aβ). Critically, LEQEMBI targets and clears the most neurotoxic form of Aβ that continuously accumulates as well as removes the existing plaques to treat this progressive, chronic disease. In June 2023, the FDA's Peripheral and Central Nervous System Drugs (PCNS) advisory committee voted unanimously that the data from Eisai's Clarity AD clinical trial confirmed the clinical benefit of LEQEMBI for the treatment of AD. Committee members also confirmed the overall risk-benefit of LEQEMBI. On January 6, 2023, LEQEMBI was approved by the FDA under the accelerated approval pathway.

Eisai has developed and deployed Understanding ARIA™, a multi-faceted educational initiative to further advance understanding in the AD healthcare community of the real-world management and monitoring of amyloid-related imaging abnormalities (ARIA). In collaboration with experts in the field of medical imaging as well as major professional societies, Understanding ARIA™ offers resources and programs that include peer-to-peer education, individual and group educational sessions and subject-matter-expert evaluation of historical case studies.

Eisai is committed to ensuring that appropriate patients have access to LEQEMBI and has established a Patient Assistance Program to provide LEQEMBI at no cost, for eligible uninsured and underinsured patients, including Medicare beneficiaries, who meet financial need and other program criteria. Additionally, Eisai offers patient support for improving access through LEQEMBI Patient Navigators, who will provide information about accessing LEQEMBI, help patients and their families understand their insurance coverage and options, and identify financial support programs for eligible patients. People in the U.S. can learn more about these services by visiting LEQEMBI.com, calling 1-833-4-LEQEMBI (1-833-453-7362), Monday-Friday, 8 a.m. to 8 p.m. Eastern Time or faxing an enrollment form to 1-833-770-7017.

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 Aβ aggregated soluble species of 75-5000 Kd.[2,3,4]

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.

IMPORTANT SAFETY INFORMATION

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES (ARIA)

- **Monoclonal antibodies directed against aggregated forms of amyloid beta, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications.**
  - **Apolipoprotein E ε4 (ApoE ε4) Homozygotes: Patients who are ApoE ε4 homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed, they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.**
- **Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI**

CONTRAINDICATION

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

AMYLOID RELATED IMAGING ABNORMALITIES

- LEQEMBI can cause ARIA-E and ARIA-H. ARIA-E can be observed on MRI as brain edema or sulcal effusions, and ARIA-H as microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H and ARIA-E can occur together. ARIA usually occurs early in treatment and 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 baseline 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 2, symptomatic ARIA occurred in 3% (29/898) of LEQEMBI-treated patients. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI. Clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation.
- Including asymptomatic radiographic events, ARIA was observed in LEQEMBI: 21% (191/898); placebo: 9% (84/897). ARIA-E was observed in LEQEMBI: 13% (113/898); placebo: 2% (15/897). ARIA-H was observed in LEQEMBI: 17% (152/898); placebo: 9% (80/897). There was no increase in isolated ARIA-H for LEQEMBI vs placebo.

ApoE ε4 Carrier Status and Risk of ARIA

- In Study 2, 16% (141/898) of patients in the LEQEMBI arm were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers.
- The incidence of ARIA was higher in ApoE ε4 homozygotes (LEQEMBI: 45%; placebo: 22%) than in heterozygotes (LEQEMBI: 19%; placebo: 9%) and noncarriers (LEQEMBI: 13%; placebo: 4%). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers.
- The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers.

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% (37/898), moderate in 7% (66/898), and severe in 1% (9/898). Resolution on MRI occurred in 52% of ARIA-E patients by 12 weeks, 81% by 17 weeks, and 100% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in LEQEMBI-treated patients was mild in 9% (79/898), moderate in 2% (19/898), and severe in 3% (28/898) of patients; superficial siderosis was mild in 4% (38/898), moderate in 1% (8/898) , and severe in 0.4% (4/898). Among LEQEMBI-treated patients, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 5% (7/141), compared to heterozygotes 0.4% (2/479) or noncarriers 0% (0/278). Among LEQEMBI-treated patients, the rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 13.5% (19/141), compared to heterozygotes 2.1% (10/479) or noncarriers 1.1% (3/278).

Intracerebral Hemorrhage

- Intracerebral hemorrhage >1 cm in diameter was reported in 0.7% (6/898) of patients in Study 2 after treatment with LEQEMBI compared to 0.1% (1/897) on placebo. Fatal events of intracerebral hemorrhage in patients taking LEQEMBI have been reported.

Concomitant Antithrombotic Medication:

- In Study 2, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Antithrombotic medications did not increase the risk of ARIA with LEQEMBI. The incidence of intracerebral hemorrhage was 0.9% (3/328 patients) in patients taking LEQEMBI with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545 patients) in those who did not receive an antithrombotic. Patients taking LEQEMBI with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 patients) compared to none in patients who received placebo.
- Because intracerebral hemorrhages >1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

Other Risk Factors for Intracerebral Hemorrhage:

- Patients were excluded from enrollment in Study 2 for findings on neuroimaging that indicated an increased risk for intracerebral hemorrhage. These included findings suggestive of cerebral amyloid angiopathy (prior cerebral hemorrhage >1 cm in greatest diameter, >4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage. The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy, which has an increased risk for intracerebral hemorrhage. Caution should be exercised when considering the use of LEQEMBI in patients with factors that indicate an increased risk for intracerebral hemorrhage and in particular for patients who need to be on anticoagulant therapy.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in LEQEMBI-treated patients. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy.

INFUSION-RELATED REACTIONS

- In Study 2, infusion-related reactions were observed in LEQEMBI: 26% (237/898); placebo: 7% (66/897), and the majority of cases in LEQEMBI-treated patients (75%, 178/237) occurred with the first infusion. Infusion-related reactions were mostly mild (69%) or moderate (28%) in severity. Infusion-related reactions resulted in discontinuations in 1% (12/898) of LEQEMBI-treated patients. 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.
- 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 2, the most common adverse reactions leading to discontinuation of LEQEMBI was ARIA-H microhemorrhages that led to discontinuation in 2% (15/898) of patients treated with LEQEMBI compared to <1% (1/897) of patients on placebo.
- In Study 2, the most common adverse reactions reported in ≥5% of patients treated with LEQEMBI (N=898) and ≥2% higher than placebo (N=897) were infusion-related reactions (LEQEMBI: 26%; placebo: 7%), ARIA-H (LEQEMBI: 14%; placebo: 8%), ARIA-E (LEQEMBI: 13%; placebo: 2%), headache (LEQEMBI: 11%; placebo: 8%), superficial siderosis of central nervous system (LEQEMBI: 6%; placebo: 3%), rash (LEQEMBI: 6%; placebo: 4%), and nausea/vomiting (LEQEMBI: 6%; placebo: 4%).

Please see full Prescribing Information for LEQEMBI, including Boxed WARNING.

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Notes to Editors

1. **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). LEQEMBI is an amyloid beta-directed antibody indicated as a disease-modifying treatment for Alzheimer's disease (AD) in the U.S. The U.S. Food and Drug Administration (FDA) granted LEQEMBI accelerated approval on January 6, 2023, and Traditional Approval on July 6, 2023. 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.

Eisai has also submitted applications for approval of lecanemab in Japan, EU, China, Canada, Great Britain and South Korea. In Japan and China, the applications have been designated for priority review, and in Great Britain, lecanemab has been designated for the Innovative Licensing and Access Pathway (ILAP), which aims to reduce the time to market for innovative medicines.

Eisai has completed a lecanemab subcutaneous bioavailability study, and subcutaneous dosing is currently being evaluated in the Clarity AD (Study 301) open-label extension (OLE). A maintenance dosing regimen has been evaluated as part of Study 201 as well as the Clarity AD (Study 301) OLE. Separate supplemental Biologics License Applications for subcutaneous dosing and a maintenance dosing regimen will be submitted to the FDA at the end of Eisai's fiscal year.

Since July 2020, the 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 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.

Since January 2022, 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, is ongoing.

2. **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 LEQEMBI development and regulatory submissions globally with both companies co-commercializing and co-promoting the product and Eisai having final decision-making authority.

3. **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.

4. **About Eisai Co., Ltd.**

Eisai's Corporate Concept is "to give first thought to patients and people in the daily living domain, and to increase the benefits that health care provides." Under this Concept (also known as *human health care* (*hhc*) Concept), we aim to effectively achieve social good in the form of relieving anxiety over health and reducing health disparities. With a global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to create and deliver innovative products to target diseases with high unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology.

In addition, we demonstrate our commitment to the elimination of neglected tropical diseases (NTDs), which is a target (3.3) of the United Nations Sustainable Development Goals (SDGs), by working on various activities together with global partners.

For more information about Eisai, please visit www.eisai.com (for global headquarters: Eisai Co., Ltd.), and connect with us on Twitter @Eisai_SDGs.

5. **About Biogen**

Founded in 1978, Biogen is a leading global biotechnology company that has pioneered multiple breakthrough innovations including a broad portfolio

of medicines to treat multiple sclerosis, the first approved treatment for spinal muscular atrophy, and two co-developed treatments to address a defining pathology of Alzheimer's disease. Biogen is advancing a pipeline of potential novel therapies across neurology, neuropsychiatry, specialized immunology and rare diseases and remains acutely focused on its purpose of serving humanity through science while advancing a healthier, more sustainable and equitable world.

The company routinely posts information that may be important to investors on its website at www.biogen.com. Follow Biogen on social media – Twitter, LinkedIn, Facebook, YouTube.

Biogen Safe Harbor
This news release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, about the potential clinical effects of lecanemab; the potential benefits, safety and efficacy of lecanemab; potential regulatory discussions, submissions and approvals and the timing thereof; the treatment of Alzheimer's disease; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai; the potential of Biogen's commercial business and pipeline programs, including lecanemab; and risks and uncertainties associated with drug development and commercialization. These statements may be identified by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "possible," "potential," "will," "would" and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical studies may not be indicative of full results or results from later stage or larger scale clinical studies and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation unexpected concerns that may arise from additional data, analysis or results obtained during clinical studies, including the Clarity AD clinical trial and AHEAD 3-45 study; the occurrence of adverse safety events; risks of unexpected costs or delays; the risk of other unexpected hurdles; regulatory submissions may take longer or be more difficult to complete than expected; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of Biogen's drug candidates, including lecanemab; actual timing and content of submissions to and decisions made by the regulatory authorities regarding lecanemab; uncertainty of success in the development and potential commercialization of lecanemab; failure to protect and enforce Biogen's data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; third party collaboration risks; and the direct and indirect impacts of the ongoing COVID-19 pandemic on Biogen's business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement as well as the risk factors identified in Biogen's most recent annual or quarterly report and in other reports Biogen has filed with the U.S. Securities and Exchange Commission. These statements are based on Biogen's current beliefs and expectations and speak only as of the date of this news release. Biogen does not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

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