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APPLICATION NUMBER:

761269Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEQEMBI™ safely and effectively. See full prescribing information for LEQEMBI™.

LEQEMBI™ (lecanemab-irmb) injection, for intravenous use

Initial U.S. Approval: 2023

INDICATIONS AND USAGE

LEQEMBI is an amyloid beta-directed antibody 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. (1)

DOSAGE AND ADMINISTRATION

- Confirm the presence of amyloid beta pathology prior to initiating treatment. (2.1)
- The recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks. (2.2)
- Obtain a recent (within one year) brain MRI prior to initiating treatment to evaluate for pre-existing Amyloid Related Imaging Abnormalities (ARIA). (2.3, 5.1)
- Obtain an MRI prior to the 5th, 7th, and 14th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms. (2.3, 5.1)
- Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection:

- 500 mg/5 mL (100 mg/mL) solution in a single-dose vial (3)
- 200 mg/2 mL (100 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Amyloid Related Imaging Abnormalities (ARIA):** Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated. (2.3, 5.1)
- Infusion-Related Reactions:** The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (at approximately 10% and higher incidence compared to placebo): infusion-related reactions, headache, and ARIA-edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of amyloid beta pathology prior to initiating treatment [see *Clinical Pharmacology (12.1)*].

2.2 Dosing Instructions

The recommended dosage of LEQEMBI is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks.

If an infusion is missed, administer the next dose as soon as possible.

2.3 Monitoring and Dosing Interruption for Amyloid Related Imaging Abnormalities

LEQEMBI can cause amyloid related imaging abnormalities -edema (ARIA-E) and -hemosiderin deposition (ARIA-H) [see *Warnings and Precautions (5.1)*].

Monitoring for ARIA

Obtain a 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 Interruptions in Patients with ARIA

ARIA-E

The recommendations for dosing interruptions for patients with ARIA-E are provided in Table 1.

Table 1: Dosing Recommendations for Patients with ARIA-E

Clinical Symptom Severity ¹	ARIA-E Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing ²	Suspend dosing ²
Mild	May continue dosing based on clinical judgment	Suspend dosing ²	
Moderate or Severe	Suspend dosing ²		

¹ Mild: discomfort noticed, but no disruption of normal daily activity.

Moderate: discomfort sufficient to reduce or affect normal daily activity.

Severe: incapacitating, with inability to work or to perform normal daily activity.

² Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

ARIA-H

The recommendations for dosing interruptions for patients with ARIA-H are provided in Table 2.

Table 2: Dosing Recommendations for Patients with ARIA-H

Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing ¹	Suspend dosing ²
Symptomatic	Suspend dosing ¹	Suspend dosing ¹	

¹ Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.

² Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue LEQEMBI.

In patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with LEQEMBI, suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgement in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue LEQEMBI.

2.4 Dilution Instructions

- Prior to administration, LEQEMBI must be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP.
- Use aseptic technique when preparing the LEQEMBI diluted solution for intravenous infusion.
- Calculate the dose (mg), the total volume (mL) of LEQEMBI solution required, and the number of vials needed based on the patient's actual body weight and the recommended dose of 10 mg/kg. Each vial contains a LEQEMBI concentration of 100 mg/mL.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check that the LEQEMBI solution is clear to opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Remove the flip-off cap from the vial. Insert the sterile syringe needle into the vial through the center of the rubber stopper.
- Withdraw the required volume of LEQEMBI from the vial(s) and add to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.
- Each vial is for one time-use only. Discard any unused portion.
- Gently invert the infusion bag containing the LEQEMBI diluted solution to mix completely. Do not shake.
- After dilution, immediate use is recommended [*see Description (11)*]. If not administered immediately, store LEQEMBI refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours, or at room temperature up to 30°C (86°F) for up to 4 hours. Do not freeze.

2.5 Administration Instructions

- Visually inspect the LEQEMBI diluted solution for particles or discoloration prior to administration. Do not use if it is discolored, or opaque or foreign particles are seen.
- Prior to infusion, allow the LEQEMBI diluted solution to warm to room temperature.
- Infuse the entire volume of the LEQEMBI diluted solution intravenously over approximately one hour through an intravenous line containing a terminal low-protein binding 0.2 micron in-line filter. Flush infusion line to ensure all LEQEMBI is administered.
- Monitor for any signs or symptoms of an infusion-related reaction. The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids [*see Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

LEQEMBI is a clear to opalescent and colorless to pale yellow solution, available as:

- Injection: 500 mg/5 mL (100 mg/mL) in a single-dose vial
- Injection: 200 mg/2 mL (100 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be

observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-H 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 of any cause and ARIA-E can occur together. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, 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.

Incidence of ARIA

Symptomatic ARIA occurred in 3% (5/161) of patients treated with LEQEMBI in Study 1 [see *Clinical Studies (14)*]. Clinical symptoms associated with ARIA resolved in 80% of patients during the period of observation.

Including asymptomatic radiographic events, ARIA was observed in 12% (20/161) of patients treated with LEQEMBI, compared to 5% (13/245) of patients on placebo in Study 1. ARIA-E was observed in 10% (16/161) of patients treated with LEQEMBI compared with 1% (2/245) of patients on placebo. ARIA-H was observed in 6% (10/161) of patients treated with LEQEMBI compared with 5% (12/245) of patients on placebo. There was no increase in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI compared to placebo.

Intracerebral hemorrhage greater than 1 cm in diameter was reported in one patient in Study 1 after treatment with LEQEMBI compared to none on placebo. Events of intracerebral hemorrhage, including fatal events, in patients taking LEQEMBI have also been reported in other studies.

ApoE ε4 Carrier Status and Risk of ARIA

In Study 1, 6% (10/161) of patients in the LEQEMBI group were apolipoprotein E ε4 (ApoE ε4) homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes and noncarriers among patients treated with LEQEMBI. Of the 5 patients treated with LEQEMBI who had symptomatic ARIA (see *Incidence of ARIA*), 4 were ApoE ε4 homozygotes, 2 of whom experienced severe symptoms. In addition, an increased incidence of symptomatic and overall ARIA in ApoE ε4 homozygotes compared to heterozygotes and noncarriers in patients taking LEQEMBI has been reported in other studies. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers [see *Dosage and Administration (2.3)*]. Consider testing for ApoE ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with LEQEMBI.

Radiographic Findings

The radiographic severity of ARIA associated with LEQEMBI was classified by the criteria shown in Table 3.

Table 3: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

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. During the study, if anticoagulant medication was used because of intercurrent medical events that required treatment for 4 weeks or less, treatment with LEQEMBI was to be temporarily suspended. Patients who received LEQEMBI and an antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) did not have an increased risk of ARIA-H compared to patients who received placebo and an antithrombotic medication. The majority of 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 greater than 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.

Additionally, patients were excluded from enrollment in Study 1 for the following risk factors for intracerebral hemorrhage: prior cerebral hemorrhage greater than 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.

Monitoring and Dose Management Guidelines

Recommendations for dosing in patients with ARIA-E depend on clinical symptoms and radiographic severity [see *Dosage and Administration* (2.3)]. Recommendations for dosing in patients with ARIA-H depend on the type of ARIA-H and radiographic severity [see *Dosage and Administration* (2.3)]. Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E.

Baseline brain MRI and periodic monitoring with MRI are recommended [see *Dosage and Administration* (2.3)]. 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.

The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including LEQEMBI. Providers may obtain information about the registry at www.alz-net.org or contact alz-net@acr.org.

5.2 Infusion-Related Reactions

In Study 1, infusion-related reactions were observed in 20% (32/161) of patients treated with LEQEMBI compared to 3% (8/245) of patients on placebo; and the majority (88%, 28/32) occurred with the first infusion. 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 include 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 patients treated with LEQEMBI had transient decreased lymphocyte counts to less than $0.9 \times 10^9/L$ compared to 2% in patients on placebo, and 22% of patients treated with LEQEMBI had transient increased neutrophil counts to greater $7.9 \times 10^9/L$ compared to 1% of patients 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.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Amyloid Related Imaging Abnormalities [*see Warnings and Precautions (5.1)*]
- Infusion-Related Reactions [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LEQEMBI has been evaluated in 763 patients who received at least one dose of LEQEMBI. In Study 1 in patients with Alzheimer's disease, 161 patients received LEQEMBI 10 mg/kg every two weeks [*see Clinical Studies (14)*]. Of these 161 patients, 44% were female, 93% were White, 6% were of Hispanic or Latino ethnicity, 4% were Asian, and 2% were Black. The mean age at study entry was 73 years (range from 51 to 88 years).

In the combined double-blind, placebo-controlled period and long-term extension period of Study 1, 237 patients received LEQEMBI for at least 6 months, 217 patients for at least 12 months, and 186 patients for 18 months.

In the double-blind, placebo-controlled period of Study 1, 15% of patients treated with LEQEMBI, compared to 6% of patients on placebo, 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.

Table 4 shows adverse reactions that were reported in at least 5% of patients treated with LEQEMBI and at least 2% more frequently than in patients on placebo.

Table 4: Adverse Reactions Reported in at Least 5% of Patients Treated with LEQEMBI 10 mg/kg Every Two Weeks and at least 2% Higher than Placebo in Study 1

Adverse Reaction	LEQEMBI 10 mg/kg Every Two Weeks N=161 %	Placebo N=245 %
Infusion-related reactions	20	3
Headache	14	10
ARIA-E	10	1
Cough	9	5
Diarrhea	8	5

Less Common Adverse Reactions

Atrial fibrillation occurred in 4% of patients treated with LEQEMBI compared to 1% in patients on placebo. Lymphopenia or decreased lymphocyte count were reported in 4% of patients treated with LEQEMBI, all after the first dose, compared to less than 1% of patients on placebo.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on LEQEMBI use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. No animal studies have been conducted to assess the potential reproductive or developmental toxicity of LEQEMBI.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

8.2 Lactation

Risk Summary

There are no data on the presence of lecanemab-irmb in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Published data from other monoclonal antibodies generally indicate low passage of monoclonal antibodies into human milk and limited systemic exposure in the breastfed infant. The effects of this limited exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEQEMBI and any potential adverse effects on the breastfed infant from LEQEMBI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of LEQEMBI in pediatric patients have not been established.

8.5 Geriatric Use

In Study 1, the age of patients exposed to LEQEMBI 10 mg/kg every two weeks ranged from 51 to 88 years, with a mean age of 73 years; 62% were 65 to 80 years, and 21% were 80 years and older. Age-related findings about clinical efficacy and safety are limited by the small numbers of patients less than 65 years of age and 80 years of age and older in clinical studies of LEQEMBI.

11 DESCRIPTION

Lecanemab-irmb is a recombinant humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta, and is expressed in a Chinese hamster ovary cell line. Lecanemab-irmb has an approximate molecular weight of 150 kDa.

LEQEMBI (lecanemab-irmb) injection is a preservative-free, sterile, clear to opalescent and colorless to pale yellow solution for intravenous use by infusion after dilution. LEQEMBI is supplied in single-dose vials available in concentrations of 500 mg/5 mL (100 mg/mL) or 200 mg/2 mL (100 mg/mL).

Each mL of solution contains 100 mg of lecanemab-irmb and arginine hydrochloride (42.13 mg), histidine (0.18 mg), histidine hydrochloride monohydrate (4.99 mg), polysorbate 80 (0.50 mg), and Water for Injection at an approximate pH of 5.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lecanemab-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. LEQEMBI reduces amyloid beta plaques, as evaluated in Study 1 [see *Clinical Studies (14)*].

12.2 Pharmacodynamics

Effect of LEQEMBI on Amyloid Beta Pathology

LEQEMBI reduced amyloid beta plaque in a dose- and time-dependent manner in Study 1, compared with placebo [see *Clinical Studies (14)*].

The effect of LEQEMBI on amyloid beta plaque levels in the brain was evaluated using PET imaging (¹⁸F-florbetapir tracer). The PET signal was quantified using the Standard Uptake Value Ratio (SUVR) method to estimate brain levels of amyloid beta plaque in composites of brain areas expected to be widely affected by Alzheimer's disease pathology (frontal, parietal, lateral temporal, sensorimotor, and anterior and posterior cingulate cortices), compared to a brain region expected to be spared of such pathology (cerebellum). The SUVR was also expressed on the Centiloid scale.

In the double-blind, placebo-controlled period of Study 1, treatment with LEQEMBI 10 mg/kg every two weeks reduced amyloid beta plaque levels in the brain, producing reductions in PET SUVR compared to placebo at both Weeks 53 and 79 (p<0.001). The magnitude of the reduction was time- and dose-dependent.

During an off-treatment period (range from 9 to 59 months; mean of 24 months), SUVR and Centiloid values began to increase with a mean rate of increase of 2.6 Centiloids/year, however, treatment difference relative to placebo at the end of the double-blind, placebo-controlled period in Study 1 was maintained.

In the double-blind, placebo-controlled period of Study 1, an increase in plasma Aβ_{42/40} ratio was observed with LEQEMBI 10 mg/kg every two weeks dosing compared to placebo.

Effect of LEQEMBI on Tau Pathophysiology

A reduction in plasma p-tau₁₈₁ was observed with LEQEMBI 10 mg/kg every two weeks compared to placebo in the double-blind, placebo-controlled period of Study 1.

Exposure-Response Relationships

Model based exposure-response analyses for Study 1 demonstrated that higher exposures to lecanemab-irmb were associated with greater reduction in clinical decline on CDR-SB and ADAS-Cog14. In addition, higher

exposures to lecanemab-irmb were associated with greater reduction in amyloid beta plaque in Study 1. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB was also observed.

Higher exposures to lecanemab-irmb were also associated with greater increase in plasma A β 42/40 ratio and greater reduction in plasma p-tau181.

12.3 Pharmacokinetics

Steady state concentrations of lecanemab-irmb were reached after 6 weeks of 10 mg/kg administered every 2 weeks and systemic accumulation was 1.4-fold. The peak concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of lecanemab-irmb increased dose proportionally in the dose range of 0.3 to 15 mg/kg following single dose.

Distribution

The mean value (95% CI) for central volume of distribution at steady-state is 3.22 (3.15-3.28) L.

Elimination

Lecanemab-irmb is degraded by proteolytic enzymes in the same manner as endogenous IgGs. The clearance of lecanemab-irmb (95% CI) is 0.434 (0.420-0.451) L/day. The terminal half-life is 5 to 7 days.

Specific Populations

Sex, body weight, and albumin were found to impact exposure to lecanemab-irmb. However, none of these covariates were found to be clinically significant.

Patients with Renal or Hepatic Impairment

No clinical studies were conducted to evaluate the pharmacokinetics of lecanemab-irmb in patients with renal or hepatic impairment. Lecanemab-irmb is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of lecanemab-irmb or of other lecanemab products.

During the 18-month treatment period in Study 1, 63/154 (40.9%) of patients treated with LEQEMBI 10 mg/kg every two weeks developed anti-lecanemab-irmb antibodies. Of these patients, neutralizing anti-lecanemab-irmb antibodies were detected in 16/63 (25.4%) patients. However, the assays used to measure anti-lecanemab-irmb antibodies and neutralizing antibodies are subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. Therefore, there is insufficient information to characterize the effects of anti-lecanemab-irmb antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted.

Mutagenesis

Genotoxicity studies have not been conducted.

Impairment of Fertility

No studies in animals have been conducted to assess the effects of lecanemab-irmb on male or female fertility. No adverse effects on male or female reproductive organs were observed in a 39-week intravenous toxicity study in monkeys administered lecanemab-irmb weekly at doses up to 100 mg/kg. The highest dose tested was associated with plasma exposures (C_{ave}) approximately 24 times that in humans at the recommended human dose (10 mg/kg every two weeks).

14 CLINICAL STUDIES

The efficacy of LEQEMBI was evaluated in a double-blind, placebo-controlled, parallel-group, dose finding study (Study 1, NCT01767311) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients] or mild dementia stage of disease [36% of patients], consistent with Stage 3 and Stage 4 Alzheimer's disease). Study 1 had a 79-week double-blind, placebo-controlled period, followed by an open-label extension period for up to 260 weeks, which was initiated after a gap period (range 9 to 59 months; mean 24 months) off treatment.

In Study 1, 856 patients were randomized to receive one of 5 doses (161 of which were randomized to the recommended dosing regimen of 10 mg/kg every two weeks) of LEQEMBI or placebo (n=247). Of the total number of patients randomized, 71.4% were ApoE ϵ 4 carriers and 28.6% were ApoE ϵ 4 non-carriers. During the study the protocol was amended to no longer randomize ApoE ϵ 4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ϵ 4 carriers who had been receiving LEQEMBI 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. As a result, in the LEQEMBI 10 mg/kg every two weeks arm, 30.3% of patients were ApoE ϵ 4 carriers and 69.7% were ApoE ϵ 4 non-carriers. At baseline, the mean age of randomized patients was 71 years, with a range of 50 to 90 years. Fifty percent of patients were male and 90% were White.

Patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater. All patients had a Mini-Mental State Examination (MMSE) score of ≥ 22 , had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale) (WMS-IV LMII). Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease.

In Study 1, a subgroup of 315 patients were enrolled in the amyloid PET substudy; of these, 277 were evaluated at week 79. Results from the amyloid beta PET substudy are described in Figure 1 and Table 5. Plasma biomarkers are described in Table 5.

Figure 1: Reduction in Brain Amyloid Beta Plaque (Adjusted Mean Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1

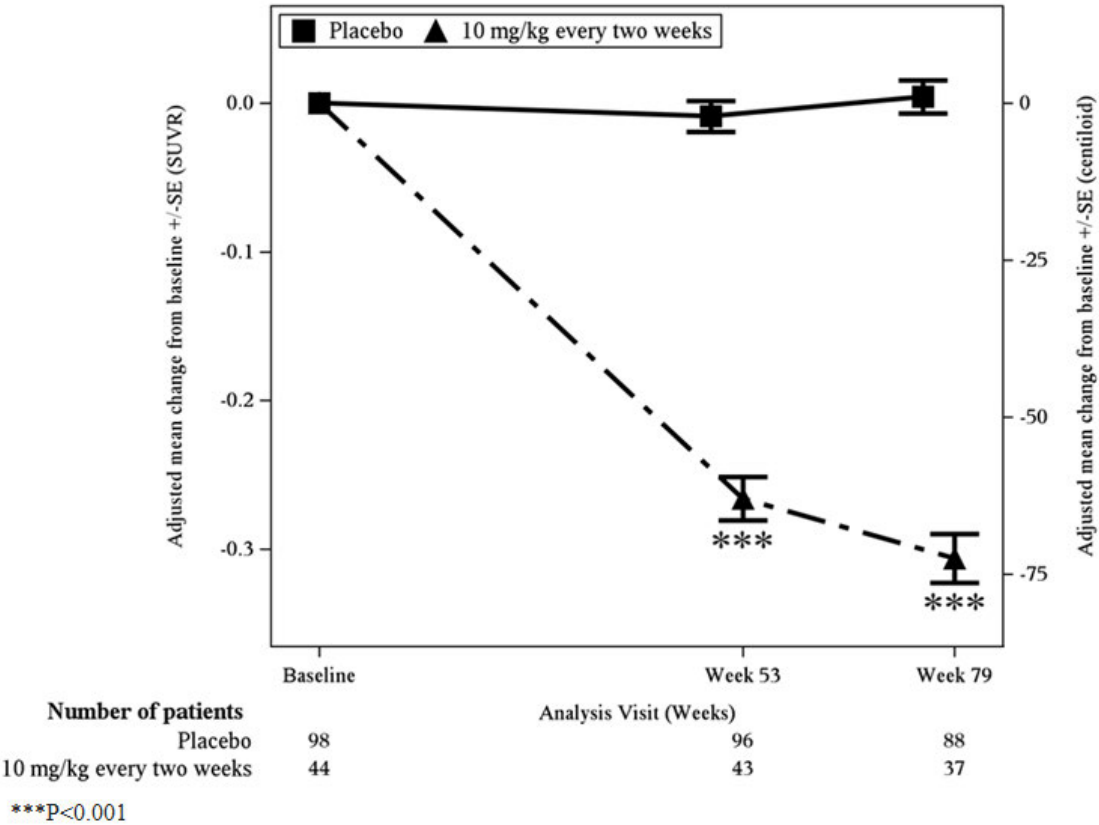


Table 5: Biomarker Results of LEQEMBI in Study 1

Biomarker Endpoints¹	LEQEMBI 10 mg/kg every two weeks	Placebo
Amyloid Beta PET Composite SUVR	N=44	N=98
Mean baseline	1.373	1.402
Adjusted mean change from baseline at Week 79 Difference from placebo	-0.306 -0.310 (p<0.001)	0.004
Amyloid Beta PET Centiloid	N=44	N=98
Mean baseline	78.0	84.8
Adjusted mean change from baseline at Week 79 Difference from placebo	-72.5 -73.5 (p<0.001)	1.0
Plasma Aβ42/40²	N=43	N=88
Mean baseline	0.0842	0.0855
Adjusted mean change from baseline at Week 79 Difference from placebo	0.0075 0.0054 (p=0.0036)	0.0021
Plasma p-tau181 (pg/mL)²	N=84	N=179
Mean baseline	4.6474	4.435
Adjusted mean change from baseline at Week 79 Difference from placebo	-1.1127 -1.1960 (p<0.0001)	0.0832

N is the number of patients with baseline value.

¹ P-values were not statistically controlled for multiple comparisons.

² Plasma Aβ42/40 and plasma p-tau181 results should be interpreted with caution due to uncertainties in bioanalysis.

The primary endpoint was change from baseline on a weighted composite score consisting of selected items from the CDR-SB, MMSE, and ADAS-Cog 14 at Week 53. LEQEMBI had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at Week 53, which did not meet the prespecified success criterion of 80%.

Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at Week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at Week 79. Results for clinical assessments showed less change from baseline in CDR-SB and ADAS-Cog 14 scores at Week 79 in the LEQEMBI group than in patients on placebo (CDR-SB: -0.40 [26%], 90% CI [-0.82, 0.03]; ADAS-Cog 14: -2.31 [47%], 90% CI [-3.91, -0.72]).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LEQEMBI (lecanemab-irmb) injection is a preservative-free, sterile, clear to opalescent, and colorless to pale yellow solution. LEQEMBI is supplied one vial per carton as follows:

500 mg/5 mL (100 mg/mL) single-dose vial (with white flip cap) – NDC 62856-215-01

200 mg/2 mL (100 mg/mL) single-dose vial (with dark grey flip cap) – NDC 62856-212-01

16.2 Storage and Handling

Unopened Vial

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).

- Store in the original carton to protect from light.
- Do not freeze or shake.

Diluted Solution

For storage of the diluted infusion solution, *see Dosage and Administration (2.5)*.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Amyloid Related Imaging Abnormalities

Inform patients that LEQEMBI may cause Amyloid Related Imaging Abnormalities or “ARIA”. ARIA most commonly presents as a temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain. Inform patients that most people with swelling in areas of the brain do not experience symptoms, however, some people may experience symptoms such as headache, confusion, dizziness, vision changes, nausea, aphasia, weakness, or seizure. Instruct patients to notify their healthcare provider if these symptoms occur. Inform patients that events of intracerebral hemorrhage greater than 1 cm in diameter have been reported infrequently in patients taking LEQEMBI, and that the use of antithrombotic or thrombolytic medications while taking LEQEMBI may increase the risk of bleeding in the brain. Notify patients that their healthcare provider will perform MRI scans to monitor for ARIA [see *Warnings and Precautions (5.1)*].

Inform patients that although ARIA can occur in any patient treated with LEQEMBI, there is an increased risk in patients who are ApoE ε4 homozygotes, and that there is a test available to determine ApoE ε4 genotype.

Patient Registry

Advise patients that the Alzheimer’s Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer’s disease, including LEQEMBI. Encourage patients to participate in the ALZ-NET registry [see *Warnings and Precautions (5.1)*].

Infusion-Related Reactions

Advise patients of the potential risk of infusion-related reactions, which can include flu-like symptoms, nausea, vomiting, and changes in blood pressure, the majority of which occur with the first infusion [see *Warnings and Precautions (5.2)*].

Manufactured by:

Eisai Inc.

Nutley, NJ 07110

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MEDICATION GUIDE
LEQEMBI™ (leh-kem'-bee)
(lecanemab-irmb)
injection, for intravenous use

What is the most important information I should know about LEQEMBI?

LEQEMBI can cause serious side effects including:

- **Amyloid Related Imaging Abnormalities or “ARIA”.** ARIA is a side effect that does not usually cause any symptoms but serious symptoms can occur. ARIA is most commonly seen as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain, and infrequently, larger areas of bleeding in the brain can occur. Most people with this type of swelling in the brain do not get symptoms, however some people may have symptoms, such as:
 - headache
 - confusion
 - dizziness
 - vision changes
 - nausea
 - difficulty walking
 - seizures

Your healthcare provider will do magnetic resonance imaging (MRI) scans before and during your treatment with LEQEMBI to check you for ARIA. Some people have a genetic risk factor (homozygous apolipoprotein E gene carriers) that may cause an increased risk for ARIA. Talk to your healthcare provider about testing to see if you have this risk factor.

Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.

What is LEQEMBI?

LEQEMBI is a prescription medicine used to treat people with Alzheimer’s disease.
It is not known if LEQEMBI is safe and effective in children.

Before receiving LEQEMBI, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if LEQEMBI will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with LEQEMBI.
- are breastfeeding or plan to breastfeed. It is not known if lecanemab-irmb (the active ingredient in LEQEMBI) passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while receiving LEQEMBI.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take medicines to reduce blood clots from forming (antithrombotic medicines, including aspirin). Ask your healthcare provider for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive LEQEMBI?

- LEQEMBI is given by a healthcare provider through a needle placed in your vein (intravenous (IV) infusion) in your arm.
- LEQEMBI is given every 2 weeks. Each infusion will last about 1 hour.
- If you miss an infusion of LEQEMBI, you should receive your next dose as soon as possible.

What are the possible side effects of LEQEMBI?

LEQEMBI can cause serious side effects, including:

- **see “What is the most important information I should know about LEQEMBI?”**
- **infusion-related reactions.** Infusion-related reactions are a common side effect which can be serious. Tell your healthcare provider right away if you get these symptoms during an infusion of LEQEMBI:
 - fever
 - flu-like symptoms (chills, body aches, feeling shaky and joint pain)
 - nausea
 - vomiting
 - dizziness or lightheadedness
 - changes in your heart rate or feel like your chest is pounding
 - difficulty breathing or shortness of breath

If you have an infusion-related reaction, your healthcare provider may give you medicines before your LEQEMBI infusions to decrease your chance of having an infusion-related reaction. These medicines may include antihistamines, anti-inflammatory medicines, or steroids.

The most common side effects of LEQEMBI include:

- infusion-related reactions
- headache
- swelling in areas of the brain, with or without small spots of bleeding in or on the surface of the brain (ARIA)

These are not all the possible side effects of LEQEMBI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of LEQEMBI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about LEQEMBI that is written for healthcare professionals.

There is a registry that collects information on treatments for Alzheimer's disease. The registry is named ALZ-NET (Alzheimer's Network for Treatment and Diagnostics). Your healthcare provider can help you become enrolled in this registry.

What are the ingredients in LEQEMBI?

Active ingredient: lecanemab-irmb.

Inactive ingredients: arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polysorbate 80, and water for injection.

Manufactured by:

Eisai Inc.

Nutley, NJ 07110

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For more information, go to www.LEQEMBI.com or call 1-888-274-2378.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: 1/2023

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO on behalf of WILLIAM H Dunn
01/06/2023 01:30:04 PM