NAME OF THE MEDICINAL PRODUCT

LEQEMBI

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 mg lecanemab

Each 2 ml vial contains 200 mg/2 ml lecanemab

Each 5 ml vial contains 500 mg/5 ml lecanemab

Guidance for Patients & Caregivers

The marketing of LEQEMBI is subject to a risk management plan (RMP) including a "Guidance for Patients & Caregivers". The "Guidance for Patients & Caregivers" emphasizes important safety information that the patient and caregiver should be aware of before and during treatment. Please explain to the patient and caregiver the need to review the guidance before starting treatment.

Prescriber guide

This product is marketed with prescriber guide providing important safety information. This includes a "Guidance for Healthcare Professionals" and an "ARIA Guidance for Radiologists". Please ensure you are familiar with this material as it contains important safety information.

WARNING: 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) 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 can occur. ARIA can be fatal. Serious intracerebral hemorrhages > 1 cm, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy to a patient being treated with LEQEMBI [see Warnings and Precautions (5.1*), Adverse Reactions (6.1)]*.

ApoE ε4 Homozygotes

Patients who are apolipoprotein E ε4 (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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.1) and Clinical Studies (11)]*.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of amyloid beta pathology prior to initiating treatment *[see Clinical Pharmacology (9)]*.

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 baseline brain magnetic resonance imaging (MRI) prior to initiating treatment with LEQEMBI. Obtain an MRI prior to the 3rd, 5th, 7th, and 14th infusions. In general, the MRI should be performed within approximately one week before the scheduled infusion of LEQEMBI and reviewed prior to proceeding with the infusion. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.

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[2]**		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[3]	Suspend dosing[3]
Mild	May continue dosing based on clinical judgment	Suspend dosing[3]	
Moderate or Severe	Suspend dosing[3]		

[1] Clinical Symptom Severity Categories:
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] See Table 3 for MRI radiographic severity *[Warnings and Precautions (5.1)]*.
[3] 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[1]**		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[3]
Symptomatic	Suspend dosing[2]	Suspend dosing[2]	

[1] See Table 3 for MRI radiographic severity *[Warnings and Precautions (5.1)]*
[2] 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.
[3] 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 judgment in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue LEQEMBI.

2.4 Preparation and Administration of LEQEMBI for Intravenous Infusion

Dilution

- Prior to administration, LEQEMBI must be diluted in 250 mL of 0.9% Sodium Chloride Injection.
- 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.
- 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 (8)]*. If not administered immediately, store LEQEMBI refrigerated at 2°C to 8°C for up to 4 hours, or at room temperature up to 30°C for up to 4 hours. Do not freeze.

Administration

- Visually inspect the LEQEMBI diluted solution for particles or discoloration prior to administration. Do not use if it is discolored, 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 (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

LEQEMBI is contraindicated in patients with hypersensitivity to lecanemab or to any of the excipients of LEQEMBI *[see Description (8)]*. Reactions have included angioedema and anaphylaxis *[see Warnings and Precautions (5.2)]*.

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 can occur spontaneously in patients with Alzheimer's disease, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. 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 usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, can occur. ARIA can be fatal. 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. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with LEQEMBI.

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.

Incidence of ARIA

Symptomatic ARIA occurred in 3% (29/898) of patients treated with LEQEMBI in Study 2 *[see Clinical Studies (11)]*. 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. Similar findings were observed in Study 1.

Including asymptomatic radiographic events, ARIA was observed in 21% (191/898) of patients treated with LEQEMBI, compared to 9% (84/897) of patients on placebo in Study 2.

In Study 2, ARIA-E was observed in 13% (113/898) of patients treated with LEQEMBI compared to 2% (15/897) of patients on placebo. ARIA-H was observed in 17% (152/898) of patients treated with LEQEMBI compared

to 9% (80/897) 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.

Incidence of Intracerebral Hemorrhage

Intracerebral hemorrhage greater than 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 observed.

Risk Factors for ARIA and Intracerebral Hemorrhage

ApoE ε4 Carrier Status

The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes.

Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygotes. 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 (45% on LEQEMBI vs. 22% on placebo) than in heterozygotes (19% on LEQEMBI vs 9% on placebo) and noncarriers (13% on LEQEMBI vs 4% on placebo). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared to 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 *[see Dosage and Administration (2.3)]*. 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. Currently available tests used to identify ApoE ε4 alleles may vary in accuracy and design.

Radiographic Findings of Cerebral Amyloid Angiopathy (CAA)

Neuroimaging findings that may indicate CAA include evidence of prior intracerebral hemorrhage, cerebral microhemorrhage, and cortical superficial siderosis. CAA has an increased risk for intracerebral hemorrhage. The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy.

The baseline presence of at least 2 microhemorrhages or the presence of at least 1 area of superficial siderosis on MRI, which may be suggestive of CAA, have been identified as risk factors for ARIA. Patients were excluded from enrollment in Study 2 for the presence of more than 4 microhemorrhages and additional findings suggestive of cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm in greatest diameter, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage.

Concomitant Antithrombotic or Thrombolytic 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.

Fatal cerebral hemorrhage has occurred in a patient taking an anti-amyloid monoclonal antibody in the setting of focal neurologic symptoms of ARIA and the use of a thrombolytic agent.

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. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with LEQEMBI.

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 , or patients with findings on MRI that are suggestive of cerebral amyloid angiopathy.

Radiographic Severity

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

In Study 2, 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) of patients, moderate in 7% (66/898) of patients, and severe in 1% (9/898) of patients. 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 patients treated with LEQEMBI 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 patients treated with LEQEMBI, 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 patients treated with LEQEMBI, 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).

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.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with LEQEMBI. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy. LEQEMBI is contraindicated in patients with a history of serious hypersensitivity to lecanemab or to any of the excipients of LEQEMBI.

5.3 Infusion-Related Reactions

In Study 2, infusion-related reactions were observed in 26% (237/898) of patients treated with LEQEMBI compared to 7% (66/897) of patients on placebo; and the majority (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 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 in Study 1, 38% of patients treated with LEQEMBI had transient decreased lymphocyte counts to less than 0.9 $x10^9$/L compared to 2% in patients on placebo, and 22% of patients treated with LEQEMBI had transient increased neutrophil counts to greater 7.9 $x10^9$/L compared to 1% of patients on placebo. Lymphocyte and neutrophil counts were not obtained after the first infusion in Study 2.

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.

5.4 Effects on ability to drive and use machines

Lecanemab has no or negligible influence on the ability to drive and use machines. Patients should be advised to use caution when driving or operating machinery in case they experience dizziness or confusion during treatment with lecanemab.

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)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*

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 2090 patients who received at least one dose of LEQEMBI. In Studies 1 and 2 in patients with Alzheimer's disease, 1059 patients received LEQEMBI 10 mg/kg every two weeks *[see Clinical Studies (11)]*. Of these 1059 patients, 50% were female, 79% were White, 15% were Asian, 12% were of Hispanic or Latino ethnicity, and 2% were Black. The mean age at study entry was 72 years (range from 50 to 90 years).

In the combined double-blind, placebo-controlled period and long-term extension period of Studies 1 and 2, 1604 patients received LEQEMBI for at least 6 months, 1261 patients for at least 12 months, and 965 patients for 18 months.

In the double-blind, placebo-controlled period in Study 1 patients stopped study treatment because of an adverse reaction in 15% of patients treated with LEQEMBI, compared to 6% patients on placebo; in Study 2 patients stopped study treatment because of an adverse reaction in 7% of patients treated with LEQEMBI, compared to 3% patients on placebo. In Study 1, 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. In Study 2, the most common adverse reaction 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.

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 in Study 1.

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

Table 5 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 in Study 2.

Table 5: 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 2

Adverse Reaction	LEQEMBI 10 mg/kg Every Two Weeks N=898%	Placebo N=897%
Infusion-related reactions	26	7
ARIA-H	14	8
ARIA-E	13	2
Headache	11	8
Superficial siderosis of central nervous system	6	3
Rash[1]	6	4
Nausea/Vomiting	6	4

[1] Rash includes acne, erythema, infusion site rash, injection site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

Less Common Adverse Reactions

Atrial fibrillation occurred in 3% of patients treated with LEQEMBI compared to 2% in patients on placebo. In Study 1, lymphopenia or decreased lymphocyte count was reported in 4% of patients treated with LEQEMBI after the first dose, compared to less than 1% of patients on placebo *[see Warnings and Precautions (5.3)]*; lymphocytes were not measured after the first dose in Study 2.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows

continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

7 USE IN SPECIFIC POPULATIONS

7.1 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.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

7.2 Lactation

Risk Summary

There are no data on the presence of lecanemab 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.

7.3 Pediatric Use

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

7.4 Geriatric Use

In Studies 1 and 2, the age of patients exposed to LEQEMBI 10 mg/kg every two weeks (n=1059) ranged from 50 to 90 years, with a mean age of 72 years; 81% were 65 years and older, and 39% were 75 years and older. No overall differences in safety or effectiveness of LEQEMBI have been observed between patients 65 years of age and older and younger adult patients.

8 DESCRIPTION

Lecanemab 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 has an approximate molecular weight of 150 kDa.

LEQEMBI (lecanemab) 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, arginine hydrochloride, histidine hydrochloride

monohydrate, polysorbate 80, histidine, and Water for Injection at an approximate pH of 5.0.

9 CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Lecanemab 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 and Study 2 *[see Clinical Studies (11)]*.

9.2 Pharmacodynamics

Effect of LEQEMBI on Amyloid Beta Pathology

The effect of LEQEMBI on amyloid beta plaque levels in the brain was evaluated using Positron Emission Tomography (PET) imaging. The PET signal was quantified using both the Standard Uptake Value Ratio (SUVR) and Centiloid scale to estimate 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).

LEQEMBI reduced amyloid beta plaque in a dose- and time-dependent manner in the dose-ranging study (Study 1) and in a time-dependent manner in single-dosing regimen study (Study 2) compared to placebo *[see Clinical Studies (11)]*.

In 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<0.0001). The magnitude of the reduction was time- and dose-dependent.

During an off-treatment period in Study 1 (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 Study 2, treatment with LEQEMBI 10 mg/kg every two weeks reduced amyloid beta plaque levels in the brain, producing reductions compared to placebo starting at Week 13 and continuing through Week 79 (P<0.0001).

An increase in plasma Aβ42/40 ratio (Table 6) and CSF Aβ[1-42] 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 (Table 6), CSF p-tau181, and CSF t-tau was observed with LEQEMBI 10 mg/kg every two weeks compared to placebo.

Table 6: Effect of LEQEMBI on Plasma Aβ42/40 and Plasma p-tau181 in Study 1 and Study 2

Biomarker Endpoints	Study 1		Study 2	
	LEQEMBI 10 mg/kg Every Two Weeks	Placebo	LEQEMBI 10 mg/kg Every Two Weeks	Placebo
Plasma Aβ42/40[2]	N=43	N=88	N=797	N=805
Mean baseline	0.0842	0.0855	0.088	0.088
Adjusted mean change from baseline at Month 18[3]	0.0075	0.0021	0.008	0.001
Difference from placebo	0.0054 (*P*=0.0036) [1]		0.007 (*P*<0.0001) [1]	
Plasma p-tau181 (pg/mL)[2]	N=84	N=179	N=746	N=752
Mean baseline	4.6474	4.435	3.696	3.740
Adjusted mean change from baseline at Month 18[3]	-1.1127	0.0832	-0.575	0.201
Difference from placebo	-1.1960 (*P*<0.0001) [1]		-0.776 (*P*<0.0001) [1]	

N is the number of patients with baseline value.
[1] P-values were not statistically controlled for multiple comparisons.
[2] Results should be interpreted with caution due to uncertainties in bioanalysis.
[3] Month 18 represents Week 79 in Study 1 and Week 77 in Study 2

A substudy was conducted in Study 2 to evaluate the effect of LEQEMBI on neurofibrillary tangles composed of tau protein using PET imaging (^{18}F-MK6240 tracer). The PET signal was quantified using the SUVR method to estimate brain levels of tau in brain regions expected to be affected by Alzheimer's disease pathology (whole cortical gray matter, meta-temporal, frontal, cingulate, parietal, occipital, medial temporal, and temporal) in the study population compared to a brain region expected to be spared of such pathology (cerebellum). The adjusted mean change from baseline in tau PET SUVR, relative to placebo, was in favor of LEQEMBI in the medial temporal (P<0.01), meta temporal (P<0.05), and temporal (P<0.05) regions. No statistically significant differences were observed for the whole cortical gray matter, frontal, cingulate, parietal, or occipital regions.

Exposure-Response Relationships

Model based exposure-response analyses demonstrated that higher exposures to lecanemab were associated with greater reduction in clinical decline on Clinical Dementia Rating scale Sum of Boxes (CDR-SB) and Alzheimer Disease Assessment Scale – Cognitive Subscale 14 (ADAS-Cog14). In addition, higher exposures to lecanemab were associated with greater reduction in amyloid beta plaque. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB and ADAS-Cog14 was also observed.

Higher exposures to lecanemab were also associated with greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181.

9.3 Pharmacokinetics

Steady-state concentrations of lecanemab 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 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 3.24 (3.18-3.30) L.

Elimination

Lecanemab is degraded by proteolytic enzymes in the same manner as endogenous IgGs. The clearance of lecanemab (95% CI) is 0.370 (0.353-0.384) 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. 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 in patients with renal or hepatic impairment. Lecanemab is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes.

9.4 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 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 antibodies. Of these patients, neutralizing anti-lecanemab antibodies were detected in 16/63 (25.4%) patients. However, the assays used to measure anti-lecanemab 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 antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.

10 NONCLINICAL TOXICOLOGY

10.1 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 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 weekly at doses up to 100 mg/kg. The highest dose tested was associated with plasma exposures (C_{ave}) approximately 27 times that in humans at the recommended human dose (10 mg/kg every two weeks).

11 CLINICAL STUDIES

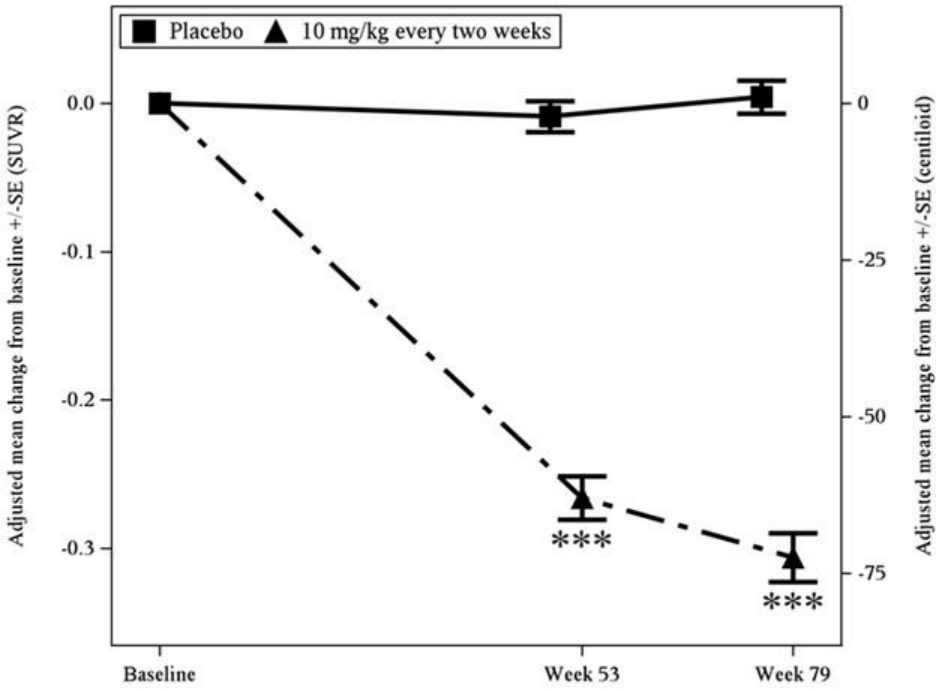
The efficacy of LEQEMBI was evaluated in two double-blind, placebo-controlled, parallel-group, randomized studies (Study 1, NCT01767311; Study 2 NCT03887455) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients in Study 1; 62% of patients in Study 2] or mild dementia stage of disease [36% of patients in Study 1; 38% of patients in Study 2], consistent with Stage 3 and Stage 4 Alzheimer's disease). In both studies, 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 and ≤30, and 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. Patients in each study could enroll in an optional, long-term extension.

Study 1

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 ε4 carriers and 28.6% were ApoE ε4 non-carriers. During the study the protocol was amended to no longer randomize ApoE ε4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ε4 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 ε4 carriers and 69.7% were ApoE ε4 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.

In Study 1, a subgroup of 315 patients were enrolled in the amyloid PET sub study; of these, 277 were evaluated at Week 79. Results from the amyloid beta PET sub study are described in Figure 1 and Table 7. Plasma biomarkers are described in Table 6.

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



***P<0.001

Table 7: Results for Amyloid Beta PET in Study 1

Biomarker Endpoints	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	-0.306	0.004
Difference from placebo	-0.310 (*P*<0.001) [1]	
Amyloid Beta PET Centiloid	N=44	N=98
Mean baseline	78.0	84.8
Adjusted mean change from baseline at Week 79	-72.5	1.0
Difference from placebo	-73.5 (*P*<0.001) [1]	

N is the number of patients with baseline value.

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

The primary endpoint was change from baseline on a weighted composite score consisting of selected items from the Clinical Dementia Rating scale Sum of Boxes (CDR-SB), MMSE, and Alzheimer Disease Assessment Scale – Cognitive Subscale 14 (ADAS-Cog14) 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-Cog14: -2.31 [47%], 90% CI [-3.91, -0.72].

After the 79-week double-blind, placebo-controlled period of Study 1, patients could enroll in 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.

Study 2

In Study 2, 1795 patients were enrolled and randomized 1:1 to receive LEQEMBI 10 mg/kg or placebo once every 2 weeks. Of the total number of patients randomized, 69% were ApoE ε4 carriers and 31% were ApoE ε4 non-carriers. Overall median age of patients was 72 years, with a range of 50 to 90 years. Fifty-two percent were women, and 1381 (77%) were White, 303 (17%) were Asian, and 47 (3%) were Black.

The randomization was stratified according to clinical subgroup (mild cognitive impairment or mild dementia stage of the disease); the presence or absence of concomitant approved therapies for Alzheimer’s disease at baseline (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine); ApoE ε4 carrier status; and geographical region.

The primary efficacy outcome was change from baseline at 18 months in the CDR-SB. Key secondary endpoints included change from baseline at 18 months for the following measures: amyloid Positron Emission Tomography (PET) using Centiloids, ADAS-Cog14, and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).

LEQEMBI treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared to placebo at 18 months (-0.45 [-27%], $P<0.0001$).

Statistically significant differences ($P<0.01$) between treatment groups were also seen in the results for ADAS-Cog14 and ADCS MCI-ADL at 18 months as presented in Table 8.

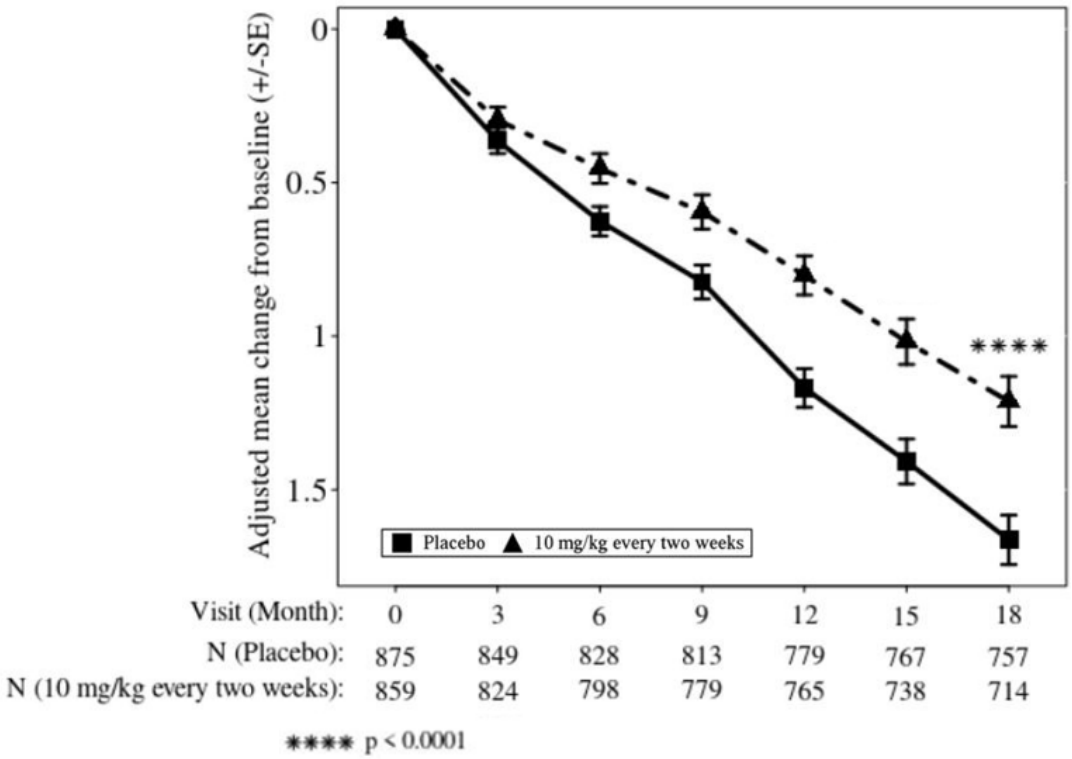
Both ApoE ε4 carriers and ApoE ε4 noncarriers showed statistically significant treatment differences for the primary endpoint and all secondary endpoints. In an exploratory subgroup analysis of ApoE ε4 homozygotes, which represented 15% of the trial population, a treatment effect was not observed with LEQEMBI treatment on the primary endpoint, CDR-SB, compared to placebo, although treatment effects that favored LEQEMBI were observed for the secondary clinical endpoints, ADAS-Cog14 and ADCS MCI-ADL. Treatment effects on disease-relevant biomarkers (amyloid beta PET, plasma Aβ42/40 ratio, plasma p-tau 181) also favored LEQEMBI in the ApoE ε4 homozygous subgroup.

Starting at six months, across all time points, LEQEMBI treatment showed statistically significant changes in the primary and all key secondary endpoints from baseline compared to placebo; see Figure 2.

Table 8: Results for CDR-SB, ADAS-Cog14, and ADCS MCI-ADL in Study 2

Clinical Endpoints	**LEQEMBI 10 mg/kg Every Two Weeks**	**Placebo**
CDR-SB	N=859	N=875
Clinical Endpoints	**LEQEMBI 10 mg/kg Every Two Weeks**	**Placebo**
Mean baseline	3.17	3.22
Adjusted mean change from baseline at 18 months (%) Difference from placebo	1.21 -0.45 (-27%) (*P*<0.0001)	1.66
ADAS-Cog14	N=854	N=872
Mean baseline	24.45	24.37
Adjusted mean change from baseline at 18 months (%) Difference from placebo	4.140 -1.442 (-26%) (*P*=0.00065)	5.581
ADCS MCI-ADL	N=783	N=796
Mean baseline	41.2	40.9
Adjusted mean change from baseline at 18 months Difference from placebo	-3.5 (-37%) 2.0 (*P*<0.0001)	-5.5

Figure 2: Adjusted Mean Change from Baseline in CDR-SB in Study 2



12 HOW SUPPLIED/STORAGE AND HANDLING

12.1 How Supplied

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

LEQEMBI 500 mg/5 mL (100 mg/mL) single-dose vial (with white flip cap)
LEQEMBI 200 mg/2 mL (100 mg/mL) single-dose vial (with dark grey flip cap)

12.2 Shelf life

The expiry date of the product is indicated on the packaging materials.

12.3 Storage and Handling

Unopened Vial

- Store in a refrigerator at 2°C to 8°C.
- 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)*.

13 REGISTRATION HOLDER AND IMPORTER

Eisai Israel Ltd., PO Box 3393, Petah Tikva, 4951600 Israel

14 REGISTRATION NUMBERS

LEQEMBI 177-01- 37811

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