▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – LEQEMBI® (LECANEMAB)

WARNINGS

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterised as ARIA with oedema (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 haemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications (see Section 4.4 Special warnings and precautions for use, Section 4.8 Adverse effects (Undesirable effects). ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke. Thrombolytic treatment should be carefully considered in this population.

ApoE ε4 Genotype

LEQEMBI is not indicated in apolipoprotein E ε4 (ApoE ε4) homozygous patients. 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 amyloid-related imaging abnormalities (ARIA) in the brain, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and non-carriers. Testing for ApoE ε4 status is required 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 (see Section 4.4 Special warnings and precautions for use).

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 Section 4.4 Special warnings and precautions for use and Section 5.1 Pharmacodynamic properties, Clinical Trials).

1 NAME OF THE MEDICINE

Lecanemab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrated injection contains 100 mg of lecanemab.

One vial of 5 mL contains 500 mg of lecanemab (500 mg/5 mL).
One vial of 2 mL contains 200 mg of lecanemab (200 mg/2 mL).

Lecanemab is a recombinant monoclonal humanised antibody produced in Chinese Hamster Ovary (CHO) cells and has a molecular weight of approximately 150 kDa.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

LEQEMBI 100 mg/mL concentrated injection is a sterile, preservative-free, clear to opalescent, colourless to pale yellow solution.

Not for direct infusion or injection (see Section 4.2 Dose and method of administration).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LEQEMBI is indicated in adult patients with a diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) that are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes.

Beta amyloid evidence consistent with Alzheimer's disease (AD) should be confirmed using a validated test prior to initiating treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's disease. LEQEMBI should be administered in specialised centres under the supervision of a multidisciplinary team trained in detection, monitoring and management of ARIA and experienced in detecting and managing infusion related reactions.

Testing for apolipoprotein E ε4 (ApoE ε4) status should be performed prior to initiation of treatment using an appropriate test. Prior to testing patients should be appropriately counselled and consented according to national or local guidelines, as applicable.

Dosage

The recommended dose of LEQEMBI is 10 mg/kg, that must be diluted then administered as an intravenous infusion over approximately one hour, once every 2 weeks (see Section 4.2 Dose and method of administration, Method of Administration).

The effectiveness of lecanemab in patients with moderate or severe Alzheimer's disease is not established; discontinue treatment if the patient progresses to moderate Alzheimer's

disease. The benefit-risk of continued treatment should be re-assessed at regular intervals on an individual basis.

The duration of the placebo-controlled efficacy studies for lecanemab was 18 months. After 18 months, cognitive function testing and clinical symptom assessment should be performed to assess whether the patient has not progressed to moderate Alzheimer's dementia and if the clinical course otherwise suggests that lecanemab has not demonstrated effectiveness in the patient, and inform the individual benefit-risk decision as to whether treatment with lecanemab should be continued beyond 18 months.

Missed Dose

If an infusion is delayed or missed, the next dose should be given as soon as possible.

Monitoring and Dosing Interruption for Amyloid Related Imaging Abnormalities

A recent (within 6 months) brain magnetic resonance imaging (MRI) should be available 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.

The recommendations for dosing interruptions for patients with amyloid-related imaging abnormalities-oedema/effusions (ARIA-E) and amyloid-related imaging abnormalities haemorrhage/hemosiderin deposition (ARIA-H) are provided in Table 1.

Table 1: Dosing Recommendations for Patients with ARIA-E and ARIA-H

Clinical Symptom	ARIA-E and ARIA-H Severity[1] on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	Consider suspending dosing	Suspend dosing	Suspend dosing
Symptomatic	Suspend dosing		

[1] See Table 2 for ARIA MRI radiographic severity

In case of asymptomatic mild ARIA, consider dose suspension based on radiological features of ARIA, number of ARIA episodes and clinical condition. In case of asymptomatic moderate or severe ARIA and symptomatic ARIA, suspend dose until MRI demonstrates radiographic resolution (ARIA-E) or stabilisation (ARIA-H) and symptoms, if present, resolve. Consider a follow-up MRI to assess for resolution (ARIA-E) or stabilisation (ARIA-H) 2 to 4 months after initial identification. Resumption of dosing or permanent discontinuation after ARIA-E resolution and ARIA-H stabilisation should be guided by clinical judgment including re-evaluation of risk factors (see Section 4.4 Special warnings and precautions for use). Standard supportive treatment, including corticosteroids may be considered in case of ARIA-E.

LEQEMBI should be permanently discontinued after serious ARIA-E, serious ARIA-H or intracerebral haemorrhage greater than 1 cm (see Section 4.3 Contraindications).

Radiographic Severity

The radiographic severity of ARIA associated with LEQEMBI was classified by the criteria shown in Table 2.

Table 2: 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 microhaemorrhage	≤ 4 new incident microhaemorrhages	5 to 9 new incident microhaemorrhages	10 or more new incident microhaemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

FLAIR: Fluid attenuated inversion recovery
ARIA-E: Amyloid-related imaging abnormalities-oedema/effusions
ARIA-H: Amyloid-related imaging abnormalities haemorrhage/hemosiderin deposition

Special Populations

Paediatric patients

There is no relevant use of LEQEMBI in the paediatric population.

Method of Administration

LEQEMBI is for intravenous use only. LEQEMBI should be administered by a healthcare professional. Prior to administration, LEQEMBI must be diluted in 250 mL of 0.9% Sodium Chloride Injection. LEQEMBI is administered as an intravenous infusion over approximately 1 hour once every 2 weeks. LEQEMBI must not be administered as an intravenous push or bolus injection.

- Calculate the dose, the total volume 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 medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Check that the LEQEMBI solution is clear to opalescent and colourless 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 centre of the rubber stopper.
- Withdraw the required volume of LEQEMBI from the vial(s) and add to an infusion bag containing 250 mL 0.9% sodium chloride solution for injection.
- Each vial is for single use in one patient 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. If not administered immediately, store LEQEMBI refrigerated at 2°C to 8°C for up to 4 hours. Do not freeze.
- Visually inspect the LEQEMBI diluted solution for particles or discolouration prior to administration. Do not use if it is discoloured, 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 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 Section 4.4 Special warnings and precautions for use).
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements (See Section 6.6 Special precautions for disposal).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

Pre-treatment MRI findings of prior intracerebral haemorrhage greater than 1 cm, more than 2 microhaemorrhages, superficial siderosis or vasogenic oedema (ARIA-E), which are suggestive of cerebral amyloid angiopathy (CAA).

Severe white matter disease.

Any finding that could prevent a satisfactory MRI evaluation for safety monitoring.

Treatment with LEQEMBI should not be initiated in patients receiving ongoing anticoagulant therapy (see Section 4.4, Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Controlled access programme

In order to promote the safe and effective use of LEQEMBI, initiation of treatment in all

patients should be through a central registration system implemented as part of a controlled access programme.

Pre-treatment screening

The efficacy and relative safety of LEQEMBI have been demonstrated in a population of patients with evidence of early Alzheimer's disease based on a clinical diagnosis of mild cognitive impairment or mild AD and confirmed amyloid deposits in the brain (see Section 5.1 Pharmacodynamic properties, Clinical Trials).

Monoclonal antibodies directed against aggregated forms of Aβ, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA). ARIA includes amyloid related imaging abnormalities-oedema/effusions (ARIA-E; also known as cerebral vasogenic oedema) and amyloid-related imaging abnormalities haemorrhage/hemosiderin deposition (ARIA-H; includes cerebral microhaemorrhage and cortical superficial siderosis). Intracerebral haemorrhage greater than 1 cm has been observed. ARIA can occur spontaneously in patients with Alzheimer's disease, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhaemorrhage or 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 of any cause and ARIA-E can occur together.

The safety of lecanemab has not been evaluated in patients with pre-treatment MRI findings suggestive of cerebral amyloid angiopathy (prior cerebral haemorrhage greater than 1 cm in greatest diameter, more than 4 microhaemorrhages, superficial siderosis, vasogenic oedema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral haemorrhage.

Apolipoprotein E (ApoE) genotype

LEQEMBI is not indicated in ApoE ε4 homozygous patients (see Section 4.1 Therapeutic indications). In Study 301, 16% (141/898) of patients in the LEQEMBI arm were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were non-carriers. 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 non-carriers (13% on LEQEMBI vs 4% on placebo). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% of non-carriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and non-carriers. The recommendations on management of ARIA do not differ between ApoE ε4 heterozygote carriers and non-carriers (see Section 4.2 Dose and method of administration). Screening for ApoE ε4 alleles prior to treatment is required.

Cerebral amyloid angiopathy

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

Amyloid-related imaging abnormalities (ARIA)

Serious cases of ARIA have been observed in lecanemab clinical studies and some have been fatal (see Section 4.8 Adverse effects (Undesirable effects)).

Most ARIA events were first observed within 6 months of initiation of treatment. Most serious ARIA events occurred within 12 weeks of treatment. Access to MRI should be available during the treatment period of LEQEMBI. An MRI should be performed prior to initiating treatment with LEQEMBI, prior to the third dose, prior to fifth dose, prior to seventh dose and prior to the fourteenth dose (see Section 4.2 Dose and method of administration). MRI may also be indicated if ARIA symptoms occur.

ARIA is often asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, may occur. When present, symptoms may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulty.

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.

Recommendations for Dosing Interruptions in Patients with ARIA

If symptoms of ARIA-H occur, it is often in the presence of ARIA-E and managed as for ARIA-E. The recommendations for dosing interruptions for patients with ARIA-E and ARIA-H are provided in Table 1 (see Section 4.2 Dose and method of administration). LEQEMBI should be permanently discontinued if serious ARIA-E, serious ARIA-H or intracerebral haemorrhage greater than 1 cm occurs (see Section 4.3 Contraindications).

Concomitant Antithrombotic Medication

Baseline use of antithrombotic medicinal products (aspirin, other antiplatelets, or anticoagulants) was allowed in clinical trials if the patient was on a stable dose. Because ARIA-H and intracerebral haemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of antithrombotic or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

· If anticoagulation needs to be commenced during therapy with lecanemab (for example

incident arterial thromboses, acute pulmonary embolism or other life threatening indications) then lecanemab should be paused. Lecanemab can be reinstated if anticoagulation is no longer medically indicated. The use of concomitant aspirin and other antiplatelet therapy is permitted.

- There was only limited exposure to thrombolytic agents in the clinical trials however the risk of severe intracranial bleed resulting from concomitant use is plausible. Use of thrombolytic agents should be avoided except for immediately life-threatening indications with no alternative management (e.g., pulmonary embolism with haemodynamic compromise) when the benefits could outweigh the risks.
- 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 lecanemab.

Patients who received LEQEMBI and an antithrombotic medicine (aspirin, other antiplatelets, or anticoagulants), did not appear to have an increased frequency of ARIA. The majority of exposures to antithrombotic medicines were to aspirin (75%). The incidence of ARIA-H was 14% (39/286) in patients taking LEQEMBI with a concomitant antithrombotic medication at the time of the event, compared to 13% (57/450) in those who did not receive an antithrombotic. The incidence of intracerebral haemorrhage 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 haemorrhage of 2.5% (2/79 patients) compared to none in patients who received placebo.

The number of events and the limited exposure to non-aspirin antithrombotic medicines limit definitive conclusions about the risk of ARIA or intracerebral haemorrhage in patients taking antithrombotic medicines.

In the long-term extension of the Phase 3 study, a fatal intracerebral haemorrhage occurred in a patient taking LEQEMBI 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.

- Treatment with lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy other than a stable dose of aspirin (see Section 4.3 Contraindications).

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.

Immunogenicity

Anti-drug antibodies (ADA) were commonly detected. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. Treatment emergent anti-lecanemab antibodies were detected in at least one serum sample in 5.5% of patients treated with LEQEMBI in Study 301. Patients with anti-lecanemab antibodies did not experience hypersensitivity reactions.

Infusion-related Reactions

Infusion-related reactions, have been observed with administration of LEQEMBI (see Section 4.8 Adverse effects (Undesirable effects)). The majority of these were mild to moderate. These reactions may be severe or life-threatening. Signs and symptoms of infusion-related reactions may include fever and flulike symptoms (chills, generalized aches, feeling shaky, and joint pain) nausea, vomiting, hypotension, hypertension, and oxygen desaturation.

In the event of an infusion 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.

Use in Hepatic Impairment

No dose adjustment is required in patients with hepatic impairment (see Section 5.2 Pharmacokinetic properties, Special , Patients with renal or hepatic impairment).

Use in Renal Impairment

No dose adjustment is required in patients with renal impairment (see Section 5.2 Pharmacokinetic properties, Special , Patients with renal or hepatic impairment).

Use in the Elderly

No clinically meaningful differences in safety or effectiveness were observed between these patients and younger patients at the recommended dose.

Paediatric Use

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

Effect on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been conducted with LEQEMBI. LEQEMBI is a monoclonal antibody (mAb) that targets soluble and insoluble aggregated forms of Aβ, and is not expected to be involved in cytokine modulated pathways.

Elimination of lecanemab is likely to occur through normal degradation pathways for immunoglobulins and the clearance should not be affected by small molecule concomitant medications. Therefore, it is not expected that lecanemab will cause or be susceptible to drug interactions with concomitantly administered agents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no data on the effects of lecanemab on human fertility. No effects on reproductive organs in cynomolgus monkeys in repeated-dose studies up to 39 weeks were noted at doses 27 times the clinical exposures (based on AUC). Because the pharmacological target of lecanemab – aggregated Aβ is not present in cynomolgus monkeys, the relevance of these data to humans is limited.

Use in Pregnancy – Pregnancy Category B2

There are no data on the use of LEQEMBI in pregnant women. No animal studies have been conducted to assess the potential reproductive or developmental toxicity of lecanemab. The risks to the developing foetus are unknown. Lecanemab is not recommended during pregnancy.

Use in Lactation

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.

A decision should be made whether to discontinue breast-feeding or to discontinue LEQEMBI, taking into account the benefit of breast-feeding for the child and the benefit of LEQEMBI therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of lecanemab on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of LEQEMBI has been evaluated in 2090 patients who received at least one dose of LEQEMBI.

In the double blind, placebo-controlled period of Study 301 in patients with Early Alzheimer's Disease a total of 898 adults received at least one dose of LEQEMBI. Study participants were administered LEQEMBI 10 mg/kg every two weeks.

Based on ApoE ε4 carrier status, of the patients treated with LEQEMBI, 31% (278/898) were non-carriers, 53% (479/898) were heterozygotes and 16% (141/898) were homozygotes.

The most frequently reported adverse reactions were infusion-related reaction (26%), ARIA-H (14%), ARIA-E (13%) and headache (11%). The most important serious adverse reactions were: serious ARIA-E (0.8%), serious ARIA-H (0.2%) and serious hypersensitivity including infusion-related reactions (1.3%).

Table 3: Treatment Emergent Adverse Events (TEAEs) Occurring in ≥ 2% of Patients in Study 301[1]

Adverse Reaction	**LEQEMBI 10 mg/kg Every Two Weeks N=898 n (%)**	**Placebo N=897 n (%)**
Cardiac disorder		
Atrial fibrillation	24 (2.7)	14 (1.6)
Gastrointestinal disorders		
Nausea	31 (3.5)	25 (2.8)
Vomiting	29 (3.2)	22 (2.5)
General disorders and administration site conditions		
Fatigue	37 (4.1)	24 (2.7)
Pyrexia	24 (2.7)	18 (2.0)
Infections and infestations		
Nasopharyngitis	36 (4.0)	35 (3.9)
Upper respiratory tract infection	25 (2.8)	19 (2.1)
Injury, poisoning and procedural complications		
Infusion-related reaction	236 (26.3)	64 (7.1)
Fall	93 (10.4)	86 (9.6)
Skin laceration	23 (2.6)	22 (2.5)
Musculoskeletal and connective tissue disorders		
Back Pain	60 (6.7)	52 (5.8)
Osteoarthritis	18 (2.0)	14 (1.6)
Nervous system disorders		
Amyloid related imaging abnormality - microhaemorrhages and haemosiderin deposits	126 (14.0)	69 (7.7)

Table 3: Treatment Emergent Adverse Events (TEAEs) Occurring in ≥ 2% of Patients in Study 301[1]

Adverse Reaction	**LEQEMBI 10 mg/kg Every Two Weeks N=898 n (%)**	**Placebo N=897 n (%)**
Amyloid related imaging abnormality - oedema/effusion	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Superficial siderosis of central nervous system	50 (5.6)	22 (2.5)

Dizziness	49 (5.5)	46 (5.1)
Syncope	18 (2.0)	12 (1.3)
Psychiatric disorders		
Anxiety	45 (5.0)	38 (4.2)
Insomnia	24 (2.7)	21 (2.3)
Renal and urinary disorder		
Haematuria	21 (2.3)	7 (0.8)
Respiratory, thoracic and mediastinal disorders		
Cough	20 (2.2)	17 (1.9)
Skin and subcutaneous tissue disorders		
Rash	52 (5.8)	37 (4.1)

Abbreviations: N = number of subjects in the analysis population; n = number of subjects with at least 1 TEAE

[1] frequency greater in lecanemab-treated patients versus placebo treated patients

Tabulated list of adverse reactions

The following Adverse Reactions listed in Table 4 below have been accumulated in clinical studies with LEQEMBI.

The adverse reactions are presented as MedDRA preferred terms under the MedDRA System Organ Class. Adverse reactions are ranked according to system organ class, using the following convention: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse Reactions

System Organ Class (SOC)	Adverse Reaction	Frequency category
Immune System Disorders	Hypersensitivity reactions[1]	Common
	Delayed hypersensitivity reactions[2,3]	Common
Nervous system disorders	Headache	Very Common
	ARIA[4]	Very Common
	ARIA-H[5,6]	Very Common
	Symptomatic ARIA-H[7]	Common
	Cerebral microhaemorrhage ≤10	Very Common
	Cerebral microhaemorrhage >10	Common
	Superficial siderosis	Common
	Intracerebral haemorrhage >1 cm	Uncommon
	ARIA-E[8,9]	Common
	Symptomatic ARIA-E[7]	Common
Cardiac disorders	Atrial fibrillation	Common
Gastrointestinal disorders	Nausea	Common
General disorders and administration site conditions	Infusion related reactions[10]	Very Common

[1] Includes angioedema, bronchospasm, anaphylaxis, rash and headache.
[2] Includes rash, headache, rhinorrhoea, rhinitis and hair loss.
[3] Occurred 24 hours after infusion.
[4] ARIA: Includes radiographic ARIA-E, symptomatic ARIA-E, radiographic ARIA-H and symptomatic ARIA-H.
[5] ARIA-H: Includes radiographic ARIA-H and symptomatic ARIA-H.
[6] ARIA-H: Amyloid related imaging abnormality-microhaemorrhage and haemosiderin deposit; Superficial siderosis of central nervous system, and Cerebellar microhaemorrhage.
[7] Includes common symptom of headache; uncommon symptoms of confusion, visual changes (diplopia, glare, vision blurred, visual acuity reduced, visual impairment), dizziness, nausea, gait difficulty and seizures.
[8] ARIA-E: Includes radiographic ARIA-E and symptomatic ARIA-E.
[9] ARIA-E is common in the indicated population and very common in the homozygote population.

[10] Includes infusion related reaction and infusion site reaction.

Description of selected adverse reactions

Amyloid-related Imaging abnormalities in the indicated population

ARIA (ARIA-E or ARIA-H) was observed in 17% (128/757) of patients treated with LEQEMBI, compared to 7% (55/764) of patients on placebo in Study 301. Symptomatic ARIA occurred in 2% (16/757) of patients on LEQEMBI. Serious ARIA events were reported for 0.5% (4/757) of patients treated with LEQEMBI.

ARIA-E was observed in 9% (67/757) of patients treated with LEQEMBI compared with 1% (10/764) of patients on placebo. The maximum radiographic severity of ARIA-E in patients on LEQEMBI was mild in 4% (31/757) of patients, moderate in 4% (33/757) of patients, and severe in 0.3% (2/757) of patients. Symptomatic ARIA-E was reported for 2% (12/757) of patients treated with LEQEMBI in Study 301. Clinical symptoms associated with ARIA-E resolved in 100% (12/12) of patients. The median time to resolution of ARIA-E was approximately 9 weeks.

ARIA-H can occur spontaneously in patients with AD independent of treatment. ARIA-H was observed in 13% (98/757) of patients treated with LEQEMBI compared with 7% (52/764) of patients on placebo. The maximum radiographic severity of ARIA-H in patients on LEQEMBI was mild in 10% (75/757) of patients, moderate in 1% (11/757) of patients, and severe in 2% (12/757) of patients. Symptomatic ARIA-H was reported for 0.8% (6/757) of patients treated with LEQEMBI compared with 0.1% (1/764) of patients on placebo. Isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) was observed in 8.1% (61/757) of LEQEMBI treated patients compared to 5.9% (45/764) on placebo.

The majority of first ARIA radiographic events in the placebo-controlled studies occurred early in treatment (within 6 months of initiation of treatment), although ARIA can occur at any time patients can have more than one episode.

Recurrence of ARIA in the Indicated Population

ARIA-E was observed in 9% (67/757) of patients on LEQEMBI, of which 88% (59/67) continued on LEQEMBI treatment with or without dose interruption. Among those that continued LEQEMBI, 14% (8/59) experienced a recurrence of ARIA-E.

ARIA-H (with or without concurrent ARIA-E) was observed in 13% (98/757) of patients on LEQEMBI and 7% (52/764) of patients on placebo, of which 80% (78/98) and 77% (40/52) continued treatment with or without dose interruption, respectively. Among those that continued, 36% (28/78) of patients on LEQEMBI and 30% (23/40) of patients on placebo experienced a recurrence of ARIA-H.

Isolated ARIA-H was observed in 8% (61/757) of patients on LEQEMBI and 6% (45/764) of patients on placebo, of which 97% (59/61) and 100% (45/45) continued treatment respectively with or without dose interruption. Among those that continued, 20% (12/59) of patients on LEQEMBI and 20% (10/45) of patients on placebo experienced a recurrence of ARIA-H.

ApoE ε4 Carrier Status and Risk of ARIA

In Study 301, the incidence of ARIA was lower in non-carriers (13% LEQEMBI vs 4% placebo) and heterozygotes (19% LEQEMBI vs 9% placebo) than in homozygotes (45% LEQEMBI vs 22% placebo). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 1% of non-carriers and 2% of heterozygotes compared with 4% of homozygotes. Serious events of ARIA occurred in approximately 1% of non-carriers and heterozygotes carriers and 3% of homozygotes. Among the patients treated with LEQEMBI, rate of severe radiographic ARIA-E was lower in non-carriers (0% (0/278)) and heterozygotes (0.4% (2/479)) compared to homozygotes (5.0% (7/141)). There was no severe radiographic ARIA-H reported.

Intracerebral Haemorrhage

In Study 301, intracerebral haemorrhage greater than 1 cm has been observed after treatment with LEQEMBI in 0.7% (6/898) of patients compared to 0.2% (2/897) for placebo. Fatal events of intracerebral haemorrhage in patients taking LEQEMBI have been observed (see Section 4.4 Special warnings and precautions for use).

Infusion related reactions

Infusion-related reactions were observed in 26% (237/898) of patients treated with LEQEMBI compared to 7% (66/897) on placebo. Serious infusion-related reactions occurred in 1% of patients treated with LEQEMBI compared to 0% on placebo.

The majority of infusion-related reactions occurred at the first dose of LEQEMBI, although they can occur at any time.

Investigations

After the first infusion in Study 201, 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 than 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 301.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

There is limited clinical experience with lecanemab overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Nervous system, psychoanaleptics, anti-dementia drugs, other anti-dementia drugs, ATC code: N06DX04

Mechanism of Action

Lecanemab is a humanised immunoglobulin gamma 1(IgG1) monoclonal antibody (mAb) that preferentially binds to large soluble Aβ protein aggregates, known as protofibrils, while still maintaining high affinity for fibrillar Aβ, which comprises amyloid plaques. The accumulation of amyloid plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Lecanemab reduces Aβ plaques, as evaluated in Study 201 and Study 301.

Pharmacodynamic Effects

Effect of LEQEMBI on Amyloid Beta Pathology

LEQEMBI reduces amyloid plaque in a time-dependent manner. The effect of LEQEMBI on amyloid plaque levels in the brain was evaluated using PET imaging (^{18}Fflorbetapir, ^{18}F-florbetaben or ^{18}F-flutemetamol tracer) visual read, and quantified using the Standard Uptake Value Ratio (SUVR) method and the Centiloid scale.

In Study 201, treatment with LEQEMBI 10 mg/kg every two weeks reduced Aβ plaque levels in the brain, producing reductions in PET SUVR compared to placebo at both Weeks 53 and 79 ($p<0.00001$). The magnitude of the reduction was time-dependent.

During an off-treatment period in Study 201 (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 201 was maintained.

In Study 201 and Study 301, an increase in plasma Aβ42/40 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 (Table 5), CSF p-tau181, and CSF t-tau was observed with LEQEMBI 10 mg/kg every two weeks compared to placebo in Study 201 and Study 301.

Table 5: Biomarker Results of LEQEMBI in Study 301 and Study 201 in the Overall Population

	Study 301		Study 201	
Biomarker Endpoints	**LEQEMBI 10 mg/kg every 2 weeks**	**Placebo**	**LEQEMBI 10 mg/kg every 2 weeks**	**Placebo**
Plasma Aβ42/40 ratio [2]	N=797	N=805	N=43	N=88
Mean Baseline	0.088	0.088	0.0842	0.0855
Adjusted mean change from Baseline at Month 18 [3]	0.008	0.001	0.0075	0.0021
Difference from placebo	0.007 (p<0.00001)[1]		0.0054 (p=0.0036)[1]	
Plasma p-tau181 (pg/mL) [2]	N=746	N=752	N=84	N=179
Mean Baseline	3.696	3.740	4.6474	4.435
Adjusted mean change from Baseline at Month 18 [3]	-0.575	0.201	-1.1127	0.0832
Difference from placebo	-0.776 (p<0.00001)[1]		-1.1960 (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 77 in Study 301 and Week 79 in Study 201

A substudy was conducted in Study 301 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 grey 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 favour 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 grey matter, frontal, cingulate, parietal, or occipital regions.

Exposure-Response Relationships

Exposure response analysis showed that observed amyloid PET SUVR decreased with the increase in lecanemab exposure. PK/PD analysis showed that changes in CSF Aβ1-42, plasma Aβ42/40 ratio and plasma p-tau181 correlated with the increase in exposure to lecanemab.

Higher exposures to lecanemab were associated with slowing of clinical decline on the CDR-

SB and ADAS-Cog14. Reduction in Aβ plaque (SUVR) was associated with slowing of clinical decline for the CDR-SB and ADAS-Cog14 at the group and individual level. Increases in plasma Aβ42/40 and decreases in plasma p-tau181 were associated with slowing of clinical decline on the same clinical scales. There were no significant covariate effects on the drug effect.

Clinical Trials

The efficacy of LEQEMBI was evaluated in two double-blind, placebo-controlled, parallel-group, randomised studies (Study 301 and Study 201) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [62% of patients in Study 301; 64% of patients in Study 201] or mild dementia stage of disease [38% of patients in Study 301; 36% of patients in Study 201]). 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 the 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.

Study 301

In Study 301, 1795 patients were enrolled and randomised 1:1 to receive LEQEMBI 10 mg/kg or placebo once every 2 weeks, of which 1521 were in the indicated population. Of the total number of patients randomised, 31% were ApoE ε4 non-carriers, 53% were heterozygotes and 16% were homozygotes. 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%) Asian, and 47 (3%) Black.

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

The primary efficacy outcome was change from baseline at 18 months in the Clinical Dementia Rating scale Sum of Boxes (CDR-SB). Key secondary endpoints included change from baseline at 18 months for the following measures: amyloid Positron Emission Tomography (PET) using centiloids, Alzheimer Disease Assessment Scale – Cognitive Subscale 14 (ADAS-cog14), Alzheimer's Disease Composite Score (ADCOMS), and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).

In the overall population, LEQEMBI treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared with placebo at 18

months (-0.45 [27%], p<0.0001).

In the indicated population (ApoE ε4 non-carriers and heterozygotes), LEQEMBI treatment reduced disease progression on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months (-0.58 [33%], p<0.00001).

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; see Table 6.

Both ApoE ε4 carriers and ApoE ε4 non-carriers 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 favoured LEQEMBI were observed for the secondary clinical endpoints, ADAS-Cog 14 and ADCS MCI-ADL.

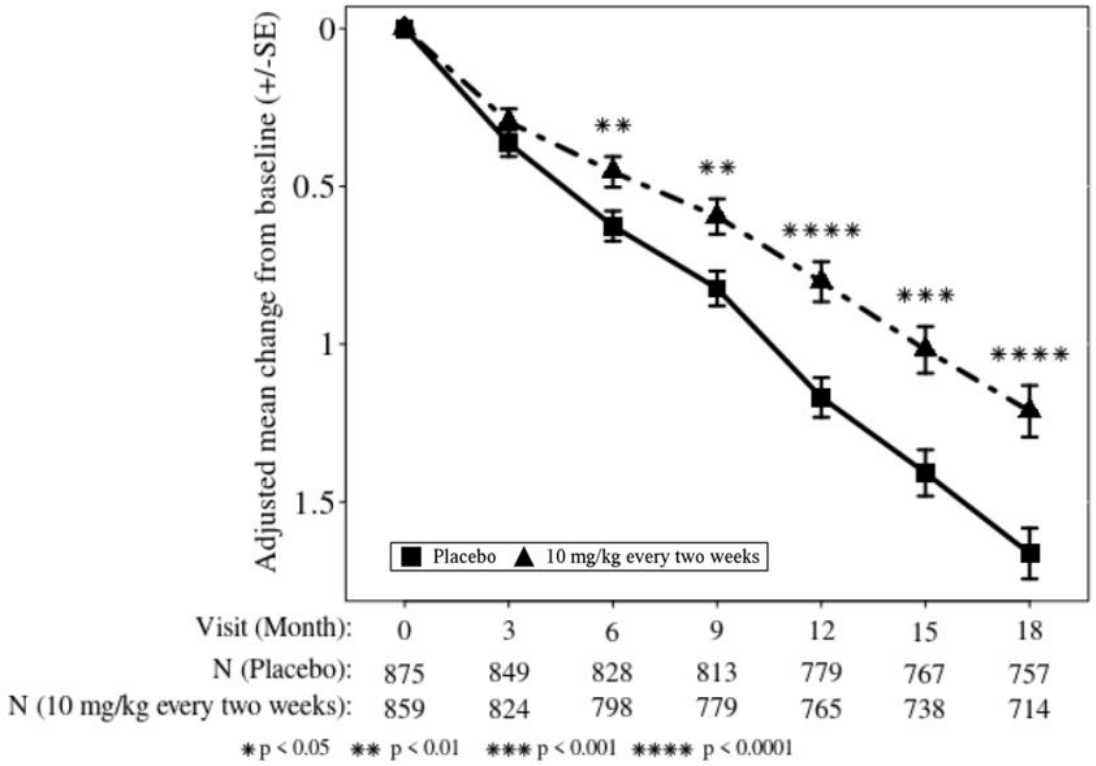
Starting at six months, across all time points, LEQEMBI treatment showed statistically significant changes in the primary and all key secondary endpoints from baseline compared to placebo (all p-values <0.01); see Figure 1.

Table 6: Results for CDR-SB, ADAS-Cog14, and ADCS MCI-ADL in Study 301

	Overall Population*	
Clinical Endpoints	**LEQEMBI 10 mg/kg every 2 weeks**	**Placebo**
CDR-SB	N=859	N=875
Mean baseline (SD)	3.17 (1.340)	3.22 (1.34)
Adjusted mean change from baseline at 18 months	1.213	1.663
Difference from placebo (95% CI)	-0.451 (-0.669, -0.233) (p=0.00005)	
ADAS-Cog14	N=854	N=872
Mean baseline (SD)	24.45 (7.082)	24.37 (7.326)
Adjusted mean change from baseline at 18 months	4.140	5.581
Difference from placebo (95% CI)	-1.442 (-2.270, -0.613) (p=0.00065)	
ADCS MCI-ADL	N=783	N=796
Mean baseline (SD)	41.2 (6.61)	40.9 (6.75)
Adjusted mean change from baseline at 18 months	-3.484	-5.500
Difference from placebo (95% CI)	2.016 (1.208, 2.823) (p<0.00001)	

* Primary analysis

Figure 1: Adjusted Mean Change from Baseline in CDR-SB in Study 301



Study 201

In Study 201, 856 patients were randomised to receive one of 5 doses (161 of which were randomised to the recommended dosing regimen of 10 mg/kg every two weeks) of LEQEMBI or placebo (n=247). Study 201 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. Of the total number of patients randomised, 71.4% were ApoE ε4 carriers and 28.6% were ApoE ε4 non-carriers. During the study the protocol was amended to no longer randomise 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 randomised patients was 71 years, with a range of 50 to 90 years. Fifty percent of patients were male and 90% were White.

The study was formally negative. The primary endpoint was change from baseline on ADCOMS, a weighted composite score consisting of selected items from the CDR-SB, MMSE, and ADAS-Cog 14 at Week 53. By Bayesian analysis, LEQEMBI had a 64% likelihood of 25% or greater reduction in 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].

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Steady state concentrations of lecanemab were reached after 6 weeks of 10 mg/kg every 2 weeks treatment 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.

Metabolism

Not applicable.

Excretion

Lecanemab is degraded by proteolytic enzymes in the same manner as endogenous IgGs. Lecanemab clearance (95% CI) is 0.370 (0.353-0.384) L/day. The terminal half-life is 5 to 7 days. Clearance was not significantly affected by immunogenicity.

Linearity/non-linearity

Lecanemab exhibits linear pharmacokinetics.

Special Populations

Age, sex, race/ethnicity and BMI

Sex and body weight were found to have effects on clearance; however, the effects were small and were not considered to be clinically relevant. Neither age nor race have an effect on clearance.

Elderly patients

There were no notable differences in the incidence of adverse reactions between these age groups, and no additional safety concerns in patients 65 years of age and older compared to younger patients.

Patients with renal or hepatic impairment

No clinical studies were conducted to evaluate the pharmacokinetics of lecanemab in patients with renal or hepatic impairment since it is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes. Liver function biomarkers (ALT, AST, ALP, total bilirubin) and creatinine clearance did not affect the PK parameters of lecanemab.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted. As a high molecular weight protein, lecanemab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

Carcinogenicity studies have not been conducted. No lecanemab related proliferative lesions were observed in toxicology studies up to 39 weeks in cynomolgus monkeys.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine
Histidine hydrochloride monohydrate
Arginine hydrochloride
Polysorbate 80
Water for Injection at an approximate pH of 5.0

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, LEQEMBI must not be prepared and infused with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After dilution, immediate use is recommended. If not used immediately, the storage period should not exceed 4 hours at 2° to 8°C.

The product is for single use in one patient only. Discard any unused portion.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C. (Refrigerate. Do not freeze).

Store in the original carton in order to protect from light.

Do not shake vials.

For storage conditions after dilution of the medicinal product, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

Glass vial with an elastomeric closure.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Lecanemab is a recombinant monoclonal IgG1 antibody which targets amyloid beta peptide (Aβ). The antibody consists of two heavy chains (HC; γ1-chains), each of 454 amino acids, and two light chains (LC; κ-chains), each of 219 amino acids.

CAS Number:

CAS Number: 1260393-98-3.

7 MEDICINE SCHEDULE (POISON STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

Eisai Australia Pty. Ltd.
Level 6, 60 City Road
Southbank, VIC, 3006

03 9832 9100
medinfo_australia@eisai.net

9 DATE OF FIRST APPROVAL

TBD

10 DATE OF REVISION

Not applicable

Summary Table of changes

Version Number	Section changed	Summary of new information
1	All	New Product Information