ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

LEQEMBI 100 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate 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 humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients with known effect
One 2 mL vial contains 1.0 mg polysorbate 80 (E 433).
One 5 mL vial contains 2.5 mg polysorbate 80 (E 433).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale yellow solution.

The solution has a pH of approximately 5.0 and an osmolality of 350-430 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leqembi is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology (see section 4.4).

4.2 Posology and method of administration

Treatment should be initiated and supervised by physicians experienced in the diagnosis and treatment of Alzheimer's disease with timely access to Magnetic Resonance Imaging (MRI). Lecanemab infusions should be administered by qualified healthcare professionals trained to monitor for, recognize and manage infusion-related reactions.

Patients treated with lecanemab must be given the patient card and be informed about the risks of lecanemab (see also package leaflet).

ApoE4 Testing

ApoE4 genotype should be assessed by a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see section 5.1).

Testing for ApoE ε4 status should be performed prior to initiation of treatment with lecanemab to inform the risk of developing ARIA (see sections 4.1 and 5.1). Prior to testing patients should be appropriately counselled and consented according to national or local guidelines, as applicable.

Posology

The recommended dose of lecanemab is 10 mg/kg body weight administered as an intravenous (IV) infusion once every 2 weeks.

Treatment with lecanemab should be discontinued once the patient progresses to moderate Alzheimer's disease.

During treatment with lecanemab, cognitive function testing and clinical symptom assessment should occur approximately every 6 months. The cognitive testing and symptom progression should be used to assess whether the patient has progressed to moderate Alzheimer's dementia, and/or if the clinical course otherwise suggests that lecanemab has not demonstrated effectiveness in the patient, and inform the decision as to whether treatment with lecanemab should be discontinued.

Monitoring for Amyloid Related Imaging Abnormalities (ARIA)

Lecanemab can cause ARIA, characterized as ARIA with oedema (ARIA-E), which can be observed on MRI as brain oedema or sulcal effusions, and ARIA with haemosiderin deposition (ARIA-H), which includes microhaemorrhage and superficial siderosis. In addition to ARIA, intracerebral haemorrhages greater than 1 cm in diameter have occurred in patients treated with lecanemab.

Obtain a recent (within 6 months) baseline brain MRI prior to initiating treatment with lecanemab to evaluate for pre-existing ARIA. Obtain an MRI prior to the 5th, 7th and 14th infusions. If a patient experiences symptoms suggestive of ARIA at any time during treatment, clinical evaluation should be performed including an MRI (see section 4.4).

Recommendations for Dosing Interruptions or Treatment Discontinuation in Patients with ARIA

ARIA-E
Dosing may continue in asymptomatic, mild radiographic ARIA-E cases. Suspend dosing for any symptomatic or radiographically moderate or severe ARIA-E. A follow-up MRI to assess for resolution 2 to 4 months after initial identification should be performed. Once the MRI demonstrates radiographic resolution and symptoms, if present, resolve, resumption of dosing should be guided by clinical judgment. See Table 1 for MRI radiographic severity (see section 4.4).

Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E. After the second occurrence of symptomatic or radiographically moderate or severe ARIA-E, treatment with lecanemab should be discontinued (see section 4.8).

ARIA-H
Dosing may continue in asymptomatic, mild radiographic ARIA-H cases. Suspend dosing for any symptomatic mild or moderate or radiographically moderate ARIA-H. A follow-up MRI to assess for stabilisation 2 to 4 months after initial identification should be performed. Once the MRI demonstrates radiographic stabilisation and symptoms, if present, resolve, resumption of dosing should be guided by clinical judgement (see section 4.8). In the event of radiographically or symptomatic severe ARIA-H, treatment with lecanemab should be permanently discontinued. See Table 1 for MRI radiographic severity (see section 4.4).

Intracerebral Haemorrhage
Lecanemab should be permanently discontinued if intracerebral haemorrhage greater than 1 cm in diameter occurs.

Delayed or missed doses
If an infusion is missed, the next dose should be administered as soon as possible.

Special populations

Elderly
No dose adjustment is necessary in patients ≥ 65 years (see section 5.1).

Renal impairment
No specific dose adjustment is necessary in patients with mild to moderate renal impairment (see section 5.2).

Hepatic impairment
No specific dose adjustment is needed for patients with mild to moderate hepatic impairment (see section 5.2).

Paediatric population
There is no relevant use of lecanemab in the paediatric population.

Method of administration

Lecanemab is for intravenous use only. Lecanemab is administered as an intravenous infusion over approximately 1 hour once every 2 weeks. For the first infusion, the patient should be observed for approximately 2.5 hours following completion of the infusion for signs and symptoms of infusion related reactions (see section 4.4).

Lecanemab is diluted prior to intravenous infusion.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Patients with bleeding disorders that are not under adequate control.

Pre-treatment MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema, or other findings, which are suggestive of cerebral amyloid angiopathy (CAA) (see section 4.4).

Treatment with lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy (see section 4.4).

4.4 Special warnings and precautions for use

Controlled access programme and registry

In order to promote the safe and effective use of lecanemab, initiation of treatment in all patients should be through a central registration system implemented as part of a controlled access programme.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with lecanemab which may be serious. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction, and initiate appropriate therapy (see section 4.2).

Amyloid beta pathology

The presence of amyloid beta pathology must be confirmed via an appropriate test prior to initiating treatment.

Amyloid Related Imaging Abnormalities (ARIA)

ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H generally occurs in association with an occurrence of ARIA-E.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. In patients who experienced ARIA on placebo or with lecanemab, 1/3 experienced recurrent ARIA. Following an initial event of ARIA, the rate of recurrence on resumption of treatment with lecanemab is very common (see section 4.8). Symptoms associated with ARIA usually resolve over time (see section 4.8).

The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygote carriers (see section 4.8). In addition to ARIA, intracerebral haemorrhages greater than 1 cm in diameter have occurred in patients treated with lecanemab.

Consider the benefit of lecanemab for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with lecanemab (see section 4.8).

Monitoring for ARIA
Baseline brain MRI and periodic monitoring with MRI are recommended. Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with lecanemab. If a patient experiences symptoms suggestive of ARIA (see section 4.8), clinical evaluation should be performed, including additional MRI testing (see section 4.2).

Radiographic Findings
The radiographic severity of ARIA associated with lecanemab was classified by the criteria shown in Table 1.

Table 1: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity[1]		
	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

[1] Radiographical severity is defined by the total number of new microhaemorrhages from baseline or total number of areas for superficial siderosis.

For patients with asymptomatic radiographic findings of ARIA-E, enhanced clinical vigilance for symptoms of ARIA is recommended (see section 4.8 for symptoms). Obtain additional MRIs after 1 to 2 months to assess for resolution, or sooner if symptoms present.

ApoE ε4 Carrier Status and Risk of ARIA
Patients treated with lecanemab who are ApoE ε4 homozygote carriers have a higher incidence of ARIA, including symptomatic serious and recurrent ARIA, compared to heterozygote carriers and non-carriers (see section 4.8). Lecanemab is not indicated for use in patients who are homozygotes (see section 4.1).

Increased Intracerebral Haemorrhage Risk
Caution should be exercised when considering the use of lecanemab in patients with factors that indicate an increased risk for intracerebral haemorrhage.

Intracerebral haemorrhages greater than 1 cm in diameter including fatal events have been observed in patients taking both lecanemab and anticoagulants or in patients receiving thrombolytic agents during lecanemab treatment. Additional caution should be exercised when considering the administration of anticoagulants to a patient already being treated with lecanemab.

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. The majority of exposures to antithrombotic medications were to aspirin. An increased risk of ARIA or intracerebral haemorrhage was not observed with antiplatelet use.

Because intracerebral haemorrhages have been observed in patients taking both lecanemab and anticoagulants (see section 4.8), and in patients receiving thrombolytic agents during lecanemab treatment, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g. tissue plasminogen activator) to a patient already being treated with lecanemab:

- 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.

Treatment with lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy (see section 4.3).

Other Risk Factors for Intracerebral Haemorrhage
Patients were excluded from enrolment in Study 301 for findings on neuroimaging that indicated an increased risk for intracerebral haemorrhage. These included findings suggestive of CAA (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.

The presence of an ApoE ε4 allele is associated with CAA, which has an increased risk for intracerebral haemorrhage.

Infusion related reactions

Infusion related reactions were observed in clinical trials with lecanemab (see section 4.8); the majority were mild or moderate and occurred with the first infusion. 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.

Patients excluded from clinical trials (see also section 5.1)

Patients with a history of transient ischemic attacks (TIA), stroke or seizures within 12 months of screening were excluded in the clinical trials with lecanemab. The safety and efficacy in these patients are unknown.

Patients with immunologic disorders who were not adequately controlled or required therapy with immunoglobulins, systemic monoclonal antibodies, systemic immunosuppressants or plasmapheresis were excluded in the clinical trials with lecanemab, hence the safety and efficacy in these patients are unknown.

Patients with autosomal dominant Alzheimer's disease or with Down syndrome may be associated with a higher rate of CAA and ARIA events and have been excluded from clinical trials with lecanemab. The safety and efficacy of lecanemab in these patients are unknown.

Patient card and patient information leaflet

The prescriber must discuss the risks of lecanemab therapy, MRI scans and signs or symptoms of adverse reactions and when to seek attention from a healthcare professional with the patient. The patient will be provided with the patient card and instructed to carry the card at all times.

Excipients with known effect

Dilution with sodium chloride (0.9% saline) is necessary before administration. See the product information for the sodium chloride diluent for information.

This medicine contains 0.5 mg of polysorbate 80 in each 1 mL of lecanemab. Polysorbates may cause allergic reactions. Patients with known allergies shall be taken into consideration.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted with lecanemab.

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 pharmacokinetic (PK) drug interactions with concomitantly administered agents.

The risk of intracerebral haemorrhage with lecanemab treatment may be increased in patients receiving anticoagulant therapy or thrombolytic agents (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Pregnancy status of females of child-bearing potential should be verified prior to initiating treatment with lecanemab.

Women of childbearing potential should use effective contraception during treatment and for 2 months after the last dose of lecanemab.

Pregnancy

There are no data on the use of lecanemab in pregnant women or animal data to assess the risk of lecanemab during pregnancy. Human IgG is known to cross the placenta after the first trimester of pregnancy. Therefore, lecanemab has the potential to be transmitted from the mother to the developing foetus. The effects of lecanemab on the developing foetus are unknown. Lecanemab is not recommended during pregnancy.

Breast-feeding

There are no data on the presence of lecanemab in human milk, the effects on the breast-fed infants, or the effects of the drugs on milk production.

Human IgG is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards. The effects of this exposure to breastfed infant are unknown and a risk cannot be excluded. Therefore, a decision should be made whether to discontinue breast-feeding or to discontinue lecanemab, taking into account the benefit of breast-feeding for the child and the benefit of lecanemab therapy for the woman.

Fertility

There are no data on the effects of lecanemab on human fertility.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

The safety of lecanemab has been evaluated in 2203 patients who received at least one dose of lecanemab.

In the double-blind, placebo-controlled period of Study 301 in patients with mild cognitive impairment due to Alzheimer’s disease or mild Alzheimer’s disease dementia, a total of 898 patients received

lecanemab at the recommended dose of 10 mg/kg every 2 weeks, of which 757 patients were non-carriers or heterozygotes (the indicated population).

Of the patients treated with lecanemab 31% (278/898) were non-carriers, 53% (479/898) were heterozygotes and 16% (141/898) were homozygotes. With the exception of events of ARIA, the safety profile was the same across genotypes.

Seizures including status epilepticus have been reported with lecanemab treatment in the clinical trials.

In the indicated population, the most common adverse reactions were infusion-related reaction (26%), ARIA-H (13%), headache (11%) and ARIA-E (9%).

Intracerebral haemorrhages greater than 1 cm in diameter were reported in 0.5% (4/757) patients in Study 301 after treatment with lecanemab compared to 0.1% (1/764) patients on placebo. Fatal events of intracerebral haemorrhage in patients receiving lecanemab have been observed.

Tabulated list of adverse reactions

The following adverse reactions listed in Table 2 below have been reported in clinical trials with lecanemab.

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, adverse reactions are presented in order of decreasing seriousness.

Table 2: 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

Incidence of ARIA in the Indicated Population

In Study 301, symptomatic ARIA occurred in 2% (16/757) patients on lecanemab who are non-carriers and heterozygotes. Serious symptoms associated with ARIA that required hospitalisation were reported in 0.4% (3/757) of patients on lecanemab. Clinical symptoms associated with ARIA resolved in 75% (12/16) of patients during the period of observation.

Including asymptomatic radiographic events, ARIA was observed in 17% (128/757) of patients on lecanemab compared to 7% (55/764) patients on placebo in Study 301.

In Study 301, ARIA-E was observed in 9% (67/757) of patients on lecanemab compared with 1% (10/764) of patients on placebo. The majority of ARIA-E was asymptomatic, with symptomatic ARIA-E reported in 2% (12/757) of patients on lecanemab and no patients on placebo. When present, reported symptoms associated with ARIA-E included headache (50%, 6/12), confusion (17%, 2/12), dizziness (8%, 1/12) and nausea (8%, 1/12). Focal neurologic deficits (8%, 1/12) also occurred.

ARIA-H was observed in 13% (98/757) of patients on lecanemab compared with 7% (52/764) of patients on placebo. The majority of ARIA-H was asymptomatic, with symptomatic ARIA-H reported in 0.8% (6/757) of patients on lecanemab and 0.1% (1/764) of patients on placebo. ARIA-H and ARIA-E can occur together. There was no increase in isolated ARIA-H (i.e. ARIA-H in patients who did not also experience ARIA-E) for lecanemab compared to placebo.

The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA-E can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients on lecanemab was mild in 4% (31/757), moderate in 4% (33/757), and severe in 0.3% (2/757) of patients. Resolution on MRI occurred in 64% (43/67) of patients by 12 weeks, 87% (58/67) by 17 weeks, and 100% (67/67) overall after detection, compared with 80% (8/10) of patients on placebo.

The maximum radiographic severity of ARIA-H microhaemorrhage in patients on lecanemab was mild in 8% (60/757), moderate in 1% (8/757), and severe in 1% (10/757) of patients; ARIA-H superficial siderosis was mild in 3% (26/757), moderate in 0.5% (4/757), and severe in 0.3% (2/757) of patients. See Table 1 in section 4.4 for MRI radiographic severity.

Recurrence of ARIA in the Indicated Population
ARIA-E was observed in 9% (67/757) of patients on lecanemab, of which 88% (59/67) continued on lecanemab treatment with or without dose interruption. Among those that continued lecanemab, 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 lecanemab 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 lecanemab 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 lecanemab 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 lecanemab and 20% (10/45) of patients on placebo experienced a recurrence of ARIA-H.

Intracerebral Haemorrhage in the Indicated Population
The incidence of intracerebral haemorrhage was 0.3% (1/286) of patients on lecanemab with a concomitant antithrombotic medication at the time of the event compared to 0.7% (3/450) of patients who did not. Patients taking lecanemab with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral haemorrhage of 1.5% (1/68 patients) compared to no patients on placebo.

ApoE ε4 Carrier Status and Risk of ARIA
Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygote carriers. In Study 301, the incidence of ARIA was lower in non-carriers (13% lecanemab vs 4% placebo) and heterozygotes (19% lecanemab vs 9% placebo) than in homozygotes (45% lecanemab vs 22% placebo). Among patients on lecanemab, ARIA-E occurred in 5% of non-carriers and 11% of heterozygotes compared with 33% of homozygotes. Symptomatic ARIA-E occurred in 1% of non-carriers and 2% of heterozygotes compared with 9% of homozygotes. ARIA-H occurred in 12% of non-carriers and 14% of heterozygotes compared with 38% of homozygotes. Symptomatic ARIA-H occurred in 1% of non-carriers and heterozygotes compared with 4% of homozygotes. Serious events of ARIA occurred in approximately 1% of non-carriers and heterozygotes carriers and 3% of homozygotes.

The recommendations on management of ARIA do not differ between ApoE ε4 carriers and non-carriers.

Infusion related reactions

Infusion-related reactions were observed in Study 301 in 26% (237/898) patients treated with lecanemab and 75% (178/237) occurred with the first infusion. Infusion-related reactions were mostly mild (69%) or moderate (28%) in severity, severe infusion-related reactions were reported in less than 1% patients. Serious infusion-related reactions have also occurred. Infusion-related reactions resulted in discontinuations in 1% (12/898) patients on lecanemab. 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). Over 63% of patients who initially experienced infusion-related reactions had no further reactions with preventative medications (see section 4.4). The incidence of infusion-related reactions was similar regardless of ApoE ε4 genotype.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There is limited clinical experience with lecanemab overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics, Other anti-dementia drugs, ATC code: N06DX04

Mechanism of action

Lecanemab is an IgG1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta and reduces amyloid beta plaques.

Pharmacodynamic effects

Effect of lecanemab on amyloid beta pathology
Lecanemab reduced amyloid beta plaque in a time-dependent manner compared with placebo. The effect of lecanemab on amyloid beta plaque levels in the brain was evaluated using PET imaging visual read, and was quantified using the Standard Uptake Value Ratio (SUVR) method and the Centiloid scale. In Study 301, the mean change from baseline relative to placebo was statistically significant for lecanemab 10 mg/kg every 2 weeks at Week 79 in the indicated population (-59.437).

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.

Immunogenicity
The immunogenicity of lecanemab has not been sufficiently evaluated due to limitation of ADA assay. The impact of ADA on pharmacokinetics, efficacy and safety has not been sufficiently evaluated.

Clinical efficacy and safety

The efficacy of lecanemab was evaluated in a double-blind, placebo-controlled, parallel-group, randomized trial (Study 301) in patients with Early Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [62% of patients] or mild dementia stage of disease [38% of patients]).

Aβ pathology was determined by visual read using approved Aβ PET tracers according to the label and CSF by total tau (t-tau)/Aβ42 ratio with the validated cut-off >0.54 (assay (assay: Lumipulse® G P-Amyloid 1-42).

Patients were enrolled with the following criteria:
- Clinical Dementia Rating (CDR) global score of 0.5, or 1.0 and a Memory Box score of 0.5 or greater
- The National Institute on Aging and the Alzheimer's Association (NIA-AA) core clinical criteria for mild cognitive impairment or probable Alzheimer's disease dementia
- Mini-Mental State Examination (MMSE) score of ≥22 and ≤30
- 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 excluded for evidence of history of transient ischemic attacks (TIA), stroke or seizures within 12 months of screening, cerebral contusion, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel or white matter disease, bleeding disorders that are not under adequate control, immunologic disorders that were not adequately controlled (e.g., active vasculitis) or required therapy with immunoglobulins, systemic monoclonal antibodies, systemic immunosuppressants or plasmapheresis.

The safety and efficacy of treatment in patients with moderate Alzheimer's disease, atypical Alzheimer's disease syndromes (without memory-predominant Alzheimer's disease), autosomal dominant Alzheimer's disease, or adults with Down syndrome is not established.

In Study 301, 1795 patients were randomized to receive lecanemab 10 mg/kg every 2 weeks or placebo for 18 months, of which 1521 were in the indicated population. Of the total number of patients randomized, 31% were non-carriers, 53% were heterozygotes and 16% were homozygotes. At baseline, the median age of randomized patients was 72 years, with a range of 50 to 90 years. Fifty-two percent of patients were women; 77% were Caucasian, 17% were Asian, and 3% were Black. Comorbidities included hyperlipidaemia (60%), hypertension (55%), obesity (17%), ischemic heart disease (16%) and diabetes (15%).

The randomization was stratified according to clinical subgroup; the presence or absence of concomitant symptomatic medication for Alzheimer's disease at baseline; ApoE ε4 carrier status; and region.

Study 301 results
The primary efficacy outcome was change from baseline at 18 months in the CDR-SB. Key secondary endpoints included change from baseline after 18 months for the following measures: amyloid PET using Centiloids, 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).

For the overall population, the difference between lecanemab and placebo in the change from baseline in CDR-SB was -0.401 (95%CI: -0.622, -0.180). The effect was similar in the overall and the indicated restricted population. Important findings from the study for the indicated population are presented in Table 3 below.

Table 3: Results for CDR-SB, ADAS-Cog14, and ADCS MCI-ADL in Study 301

	Indicated Population	
Clinical Endpoints	**Lecanemab 10 mg/kg every 2 weeks**	**Placebo**
CDR-SB	N=757	N=764
Mean baseline (SD)	3.18 (1.346)	3.23 (1.343)
Adjusted mean change from baseline at 18 months Difference from placebo (95% CI)	1.217 -0.535 (-0.778, -0.293)	1.752
ADAS-Cog14	N=757	N=764
Mean baseline (SD)	24.46 (7.081)	24.40 (7.576)
Adjusted mean change from baseline at 18 months Difference from placebo (95% CI)	4.389 -1.512 (-2.486, -0.538)	5.901
ADCS MCI-ADL	N=757	N=764
Mean baseline (SD)	41.15 (6.616)	40.72 (6.937)
Adjusted mean change from baseline at 18 months Difference from placebo (95% CI)	-3.873 1.936 (1.029, 2.844)	-5.809

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with lecanemab in all subsets of the paediatric population in early Alzheimer's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The PK of lecanemab was characterized using a population PK analysis with concentration data collected from 1619 patients with Alzheimer's disease who received lecanemab in single or multiple doses. Steady state concentrations of lecanemab were reached after 6 weeks of 10 mg/kg every 2 weeks treatment and systemic accumulation was approximately 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.

Absorption

Not applicable.

Distribution

The mean value (95% CI) for volume of distribution at steady state is 5.52 (5.14 – 5.93) L.

Biotransformation

Lecanemab is a mAb that targets soluble and insoluble aggregated forms of amyloid beta, and is not expected to be involved in cytokine modulated pathways.

Elimination

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.

Linearity/non-linearity

Lecanemab exhibits linear pharmacokinetics.

Hepatic or renal impairment

Lecanemab elimination occurs through normal degradative pathways for immunoglobulins, and the systemic clearance should not be affected by renal or hepatic impairment. Liver function biomarkers (ALT, AST, ALP, total bilirubin) and creatinine clearance did not affect the PK parameters of lecanemab.

5.3 Preclinical safety data

Carcinogenesis

Carcinogenicity studies have not been conducted.

Mutagenesis

Genotoxicity studies have not been conducted.

Developmental and reproductive toxicity

No studies in animals have been conducted to assess the effects of lecanemab on male or female fertility or developmental and reproductive function. 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 (corresponding to plasma exposures 27-fold higher than in humans at the recommended dose). The relevance of these data to humans is limited since aggregate Aβ species are not present in healthy monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine (for pH-adjustment)
Histidine hydrochloride monohydrate (for pH-adjustment)
Arginine hydrochloride
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened vial: 42 months.

After preparation of the infusion solution.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C.
From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

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

Do not freeze or shake vials.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 mL of concentrate containing 200 mg lecanemab in a 6 mL vial (Type I clear glass), with a stopper (chlorobutyl) and a seal (aluminium) with a dark grey flip-off cap, in a pack size of 1.

5mL of concentrate containing 500 mg lecanemab in a 6 mL vial (Type I clear glass), with a stopper (chlorobutyl) and a seal (aluminium) with a white flip-off cap, in a pack size of 1.

Each carton contains one vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. In the event of either being observed, discard the medicinal product.

Preparation of infusion solution
Calculate the dose, the total volume of lecanemab solution required, and the number of vials needed based on the patient's actual body weight. Each vial contains a lecanemab concentration of 100 mg/mL.

Withdraw the required volume of lecanemab from the vial(s) and add to 250 mL 0.9% sodium chloride solution for injection.

Gently invert the infusion bag containing the lecanemab diluted solution to mix completely. Do not shake.

Infusion bags manufactured using polypropylene, polyvinyl chloride, co-extruded polyolefin/polyamide, or ethylene/propylene copolymer have been confirmed to be compatible for administration of lecanemab.

After dilution, immediate use is recommended.

Administration of infusion solution
Prior to infusion, allow the lecanemab diluted solution to warm to room temperature.

Infuse the entire volume of lecanemab intravenously over approximately 1 hour through an intravenous line containing a terminal low-protein binding 0.2 micron in-line filter (compatible filter materials include polytetrafluoroethylene, polyethersulfone, polycarbonate, polyvinylidenedifluoride, polypropylene, polyurethane and polysulfone). Flush infusion line to ensure all lecanemab is administered.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 360549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

8. MARKETING AUTHORISATION NUMBER

EU/1/24/1891/001
EU/1/24/1891/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 April 2025

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Biogen International GmbH
Attisholzstrasse 11
Luterbach
So
4542
Switzerland

Name and address of the manufacturer responsible for batch release

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State prior to LEQEMBI being marketed, all healthcare professionals and patients who are expected to prescribe or use LEQEMBI have access to/are provided with the following educational package which should be agreed with the National Competent authorities of those member states:

- **Guide for healthcare professionals**

The Guide for healthcare professionals should contain the following key elements:

- Statement outlining there is a controlled access program.
- Statement that all EU lecanemab patients must be registered in the registry and brief information on how to enrol patients.
- Contraindications.
- Information on ARIA, including what it is, incidence and symptoms (ARIA-E and ARIA-H (microhaemorrhages and superficial siderosis).
- ARIA Intracerebral haemorrhage >1 cm in diameter including what it is, incidence, and use of concomitant antithrombotic medication.
- Activities to be undertaken prior to treatment including baseline MRI and *APOE4* testing.
- How to identify and manage ARIA through MRI monitoring, radiographic severity criteria, and the treatment recommendations (can be adjusted based on the national clinical practice).
- Patients who are homozygous *APOE4* carriers have a higher incidence of ARIA when treated with monoclonal antibodies directed against aggregated forms of Aβ, including lecanemab, compared to heterozygous *APOE4* carriers and noncarriers. Lecanemab is not indicated for use in homozygous *APOE4* carriers.
- Statement that ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke.
- Package Leaflet and Patient Card must be given to the patient/caregiver.
- Reminder of how and where to report side effects.
- Lists of tests to be conducted for the initial screening of the patient:
    - The patient has a clinical diagnosis of MCI due to Alzheimer's disease or Mild Alzheimer's disease, including the presence of amyloid beta pathology. A recent (within 6 months) baseline brain MRI has been obtained prior to initiating treatment with Leqembi.
    - *APOE* ε4 (gene) (understanding *APOE* ε4 genotype is important to identify appropriate patients to treat).
    - No findings suggestive of CAA on pre-treatment MRI.
    - Organisation of appointments of follow up MRI scans.

- **Patient Card**

The Patient Card should contain the following key elements:

- Request to read the package leaflet.
- Summary of what Leqembi is used for.
- Information that treatment with Leqembi should not be initiated in patients receiving ongoing anticoagulant therapy.
- Information on how Leqembi is administered, time management of administration and information about the need and number of MRI scans.
- A warning message for physicians treating the patient at any time, including in conditions of emergency, that the patient is using lecanemab.
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional.

- **Controlled Access Program**

The MAH shall agree to the details of a Controlled Access Program with each National Competent Authority and must implement such programme nationally to ensure that a Controlled Access Programme (CAP) promotes the safe and effective use of lecanemab and prevents off-label use.

The Controlled Access Program includes the following key principles that will be incorporated within each system in all Member States. These are:

- Each HCP will be registered separately before they are able to enroll patients in the CAP. As part of the HCP registration process, HCPs will be required to confirm that they have been provided with and understand the Guide for Healthcare Professionals and the SmPC and that they meet requirements to comply with the resticted medicinal prescription status (described in the section 4.2 of the SmPC).
- Treatment in all patients should be initiated through an imposed central registration system. The system will ensure appropriate and relevant information on the specified data fields (such as amyloid pathology, MCI or mild AD, *APOE4* genotype, MRI, history of cerebral haemorrhage, anticoagulant therapy, patient card and PIL, acknowledgment of risks) prior to the first infusion of lecanemab, for all patients.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
EU Lecanemab All-Patient Study	Draft protocol: January 2025 Final protocol: March 2025 Progress Reports: Annually starting September 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

LEQEMBI 100 mg/mL concentrate for solution for infusion
lecanemab

2. STATEMENT OF ACTIVE SUBSTANCE

Each mL of solution contains 100 mg of lecanemab.
One vial of 2 mL contains 200 mg of lecanemab
One vial of 5 mL contains 500 mg of lecanemab

3. LIST OF EXCIPIENTS

Excipients: arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polysorbate 80, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
1 vial of 2 mL
1 vial of 5 mL

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP
After dilution, the product should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light
Store in a refrigerator
Do not freeze or shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH,
Edmund-Rumpler-Straße 3,
60549 Frankfurt am Main,
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1891/001 200 mg vial
EU/1/24/1891/002 500 mg vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LEQEMBI 100 mg/mL concentrate for solution for infusion
lecanemab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/2 mL
500 mg/5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

LEQEMBI 100 mg/mL concentrate for solution for infusion
lecanemab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the patient card with you at all times.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LEQEMBI is and what it is used for

What LEQEMBI is
LEQEMBI contains the active substance lecanemab. It belongs to a group of medicines called anti-dementia medicines which are used to treat Alzheimer's disease. Lecanemab is a monoclonal antibody. These medicines act like the antibodies that your body makes naturally. They work by sticking to harmful target proteins, stimulating the body's immune system to get rid of the proteins. Lecanemab binds to a protein called *amyloid beta*, which is involved in Alzheimer's disease.

Who could take LEQEMBI
LEQEMBI is used to treat mild cognitive impairment or mild dementia due to Alzheimer's disease (also known as Early Alzheimer's disease) in adults who carry one copy of a gene called apolipoprotein E4, also known as ApoE4, or in adults who do not carry this gene. Your doctor will perform testing to make sure that LEQEMBI is right for you.

How LEQEMBI works
Alzheimer's disease is an illness that affects the brain. Amyloid beta clumps damage brain cells and stop them functioning normally. This eventually leads to problems with memory, thinking and behaviour. Alzheimer's disease symptoms can be different for everyone. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks.

LEQEMBI works by sticking to these clumps and reducing them. For patients with mild cognitive impairment, LEQEMBI could delay the onset of dementia. For people with mild dementia, LEQEMBI may slow the development of more severe symptoms.

2. What you need to know before you use LEQEMBI

Do not use LEQEMBI
- if you are allergic to lecanemab or any of the other ingredients of this medicine (listed in section 6).

– if you have a bleeding disorder that is not being controlled.
– if your Magnetic Resonance Imaging (MRI), a medical imaging technique that uses a magnetic field and computer-generated radio waves to create detailed images of the organs and tissues in your body, brain scan shows small spots of bleeding or fluid in the brain or evidence of larger bleeding in the past.
– If you are receiving medicines (called anticoagulants) to prevent blood clots.

Warnings and precautions

Allergic reactions

Immediately tell the healthcare professional giving you LEQEMBI if you get an allergic reaction during or shortly after you are given LEQEMBI. See section 4 for signs of an allergic reaction.

Amyloid related imaging abnormalities (ARIA)

LEQEMBI can cause a side effect called amyloid related imaging abnormalities, or "ARIA". There are two main types of ARIA:
– The build-up of fluid in one or more areas of the brain (this is called ARIA-E).
– Spots of bleeding in the brain, or on the surface of the brain (this is called ARIA-H).

Most people with ARIA do not experience symptoms. ARIA symptoms may occur in 2 out of 100 people. Symptoms include headache, confusion, dizziness, blurry vision, feeling sick (nausea), difficulty walking or seizures (fits). In a small number of people (less than 1 out of 100 people), these symptoms may be severe.

Contact your doctor urgently if you experience any of these symptoms.

ARIA is visible on an MRI brain scan.

Your doctor will arrange MRI scans before your fifth, seventh and fourteenth doses of LEQEMBI. This is routine safety monitoring to check if you have ARIA. Additional scans might be performed at any time during treatment if your doctor thinks you need them.

Your doctor may stop treatment with LEQEMBI temporarily or permanently, depending on your MRI results.

Genetic risk factors for ARIA

Some people carry a gene called "apolipoprotein E4", also known as ApoE4. This means they may be at higher risk of ARIA. Your doctor can arrange a genetic test for ApoE4, to see if you are a carrier, and if you are at higher risk of ARIA.

Medicines used to prevent or dissolve blood clots

The risks of having a larger bleed in the brain (known as intracerebral haemorrhage) with LEQEMBI treatment is increased in patients receiving medicines used to prevent blood clots (anticoagulants) or to dissolve them (thrombolytic agents). Tell your doctor that you are being treated with LEQEMBI before you receive any medication to prevent blood clots or dissolve them. LEQEMBI can be used together with aspirin and other medicines that prevent your blood cells sticking together (antiplatelet agents).

Infusion-related reactions

Infusion-related reactions are a very common side effect which can be serious (see section 4 for symptoms). If you have an infusion-related reaction, you may be given medicines before your infusions to decrease your chance of having an infusion-related reaction. These medicines may include

antihistamines, paracetamol, anti-inflammatory medicines or steroids. You will be observed for 2.5 hours after your first infusion to monitor for any signs of an infusion-related reaction.

Autosomal Dominant Alzheimer's disease and adults with Down syndrome

The use of LEQEMBI in the treatment of Autosomal Dominant Alzheimer's disease and in adults with Down syndrome has not been established.

Mini stroke (transient ischemic attack, TIA), stroke or seizures

Tell your doctor before you are given LEQEMBI if you have had a mini stroke (TIA), stroke or seizure (fit) within the last 12 months. The use of LEQEMBI in patients who have had a mini stroke, stroke or seizure in the past has not been established.

Patients with lowered immune response or taking immunosuppressants

Tell your doctor before you are given LEQEMBI if you have an immunological disorder or if you take any other medicines by injection or medicines that suppress your immune system. The use of LEQEMBI in patients who have a suppressed immune system has not been established.

Children and adolescents
LEQEMBI is not for use in children and adolescents aged less than 18 years.

Other medicines and LEQEMBI
Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular tell your doctor:

- If you are taking medicines (called anticoagulants) that prevent blood clots. LEQEMBI must not be used with these medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine. It is not known if LEQEMBI will harm your unborn baby.

If you are a woman who could become pregnant, you should use contraception during treatment with LEQEMBI and up to 2 months after the last dose of LEQEMBI. The absence of pregnancy will be verified before receiving the treatment.

If you become pregnant while you are using LEQEMBI, tell your doctor. The use of LEQEMBI is not recommended if you are pregnant.

If you are breastfeeding, you and your doctor can discuss if you should carry on with breastfeeding or treatment. It is not known if LEQEMBI passes into breast milk.

Driving and using machines
When taking LEQEMBI, some patients may experience symptoms such as dizziness or confusion. This could affect the ability to drive and use machines. If you are experiencing these side effects due to LEQEMBI, ask your doctor whether you can continue to drive and use machines.

LEQEMBI contains polysorbate 80
This medicine contains 0.5 mg of polysorbate in each 1 mL of LEQEMBI. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

This medicine contains no sodium but the concentrate needs to be diluted with sodium chloride solution, to be taken into consideration for daily dietary intake of sodium.

Patient card
You will also find key messages from this package leaflet on the patient card you have been given by your doctor. It is important that you keep this patient card at all times and show it to your partner or caregivers.

3. How to use LEQEMBI

LEQEMBI will be given to you under the supervision of a healthcare professional.

Dosage
The recommended dose is 10 milligrams per kilogram of your body weight (mg/kg). It should be given to you every 2 weeks.

LEQEMBI is given as a 'drip' (a needle placed in your vein) also called an intravenous (IV) infusion. Each infusion will last approximately 1 hour.

If you miss an infusion of LEQEMBI
If you miss an infusion of LEQEMBI, talk to your doctor to arrange to have it as soon as possible. Do not wait until your next planned infusion.

When to stop using LEQEMBI
Your doctor may recommend pausing or stopping treatment, depending on your clinical test results, if you develop ARIA, or experience other side effects.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported with LEQEMBI:

Serious side effects

Up to 1 in 10 people may experience the following side effect:
– An allergic reaction while or shortly after you are given this medicine. Signs of an allergic reaction include swelling underneath the skin, difficulty breathing caused by narrowing of the airways, serious potentially life-threatening allergic reaction, rash and headache.

Up to 1 in 100 people may experience the following side effect:
– Large areas of bleeding in the brain (known as intracerebral haemorrhages). This can cause symptoms including severe headaches, confusion, seizures or stroke.

Contact your doctor urgently if you experience these side effects.

Other side effects

Over 1 in 10 people may experience the following side effects:
– Infusion-related reactions. Signs include fever, flu-like symptoms such as chills, body aches, feeling shaky and joint pain, feeling sick (nausea), being sick (vomiting), low blood pressure, high blood pressure or low oxygen in your blood which can cause difficulty breathing or shortness of breath, changes in your heart rate, feeling like your chest is pounding or restlessness.
– Headache.

– ARIA. Signs of ARIA include headache, confusion, dizziness, blurry vision, feeling sick (nausea), difficulty walking or seizures (fits). One of two main types of ARIA, ARIA-H is linked to small areas of bleeding in the brain.

Up to 1 in 10 people may experience the following side effects:
– Delayed allergic reactions. Signs include rash, headache, runny nose, and hair loss.
– ARIA-E, linked to temporary fluid build-up in one or more regions of the brain. See signs of ARIA above.
– Abnormal heart rhythm (this is called atrial fibrillation). Signs include irregular heartbeat (racing or fluttering in your chest), chest pain, shortness of breath, dizziness or feeling faint, tiredness, or finding it harder to exercise.
– Feeling sick (nausea).

Talk to your doctor about how to manage these side effects.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LEQEMBI

– Keep this medicine out of the sight and reach of children.
– Do not use this medicine after the expiry date which is stated on the carton and the vial label after 'EXP'. The expiry date refers to the last day of that month.
– Store in the original package in order to protect from light.
– Store in a refrigerator (2 °C - 8 °C). Do not freeze or shake.
– After dilution, an immediate use is recommended. Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C. From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not use immediately, in-use storage times and conditions are the responsibility of the user.

6. Contents of the pack and other information

What LEQEMBI contains
– The active substance is lecanemab. Each mL of concentrate contains 100 mg lecanemab.
– The other ingredients are water for injections, histidine hydrochloride monohydrate, arginine hydrochloride and polysorbate 80.

What LEQEMBI looks like and contents of the pack
LEQEMBI is a concentrate for solution for infusion. Each carton contains 1 vial of 2 ml concentrate or 1 vial of 5 ml concentrate. The concentrate is clear to slightly opalescent, colourless to pale yellow.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Eisai GmbH
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e-mail: medinfo_de@eisai.net

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:
See section 3 for Posology of the medicine.

Instructions for preparation

LEQEMBI is for single use only.

LEQEMBI is a concentrate and must be diluted prior to infusion.

Calculating the dose
More than one vial of LEQEMBI concentrate may be needed to give the total dose for the patient.

The prescribed dose for the patient is given in mg/kg (see section 3). Based on this prescribed dose, calculate the total dose to be given.

The total LEQEMBI dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.

The volume of LEQEMBI concentrate to prepare the dose (mL) = the total dose in mg, divided by 100 (the LEQEMBI concentrate strength is 100 mg/mL).

Preparing the LEQEMBI infusion
Aseptic technique should be used when preparing the LEQEMBI diluted solution for intravenous infusion.

- Check that the LEQEMBI liquid is clear to slightly opalescent and colourless to pale yellow.
- Withdraw the required volume of LEQEMBI from the vial(s) and add to 250 mL 0.9% sodium chloride solution for injection.
- Gently invert the infusion bag containing the LEQEMBI diluted solution to mix completely. Do not shake.
- Infusion bags manufactured using polypropylene, polyvinyl chloride, co-extruded polyolefin/polyamide, or ethylene/propylene copolymer have been confirmed to be compatible for administration of lecanemab.
- After dilution, an immediate use is recommended. Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C. From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
- Prior to infusion, allow the LEQEMBI diluted solution to warm to room temperature.
- Any unused product or waste material should be disposed of in accordance with local requirements.

Method of administration
LEQEMBI is for intravenous use only.

LEQEMBI is diluted prior to intravenous infusion (as per above instructions for preparation).

The diluted medicinal product should be visually inspected for particles or discolouration prior to administration. Do not use if it is discoloured or if opaque particles are seen.

The diluted solution is infused through an intravenous line over approximately 1 hour. Use of a sterile, low-protein binding 0.2 micron in-line filter (compatible filter materials include polytetrafluoroethylene, polyethersulfone, polycarbonate, polyvinylidenedifluoride, polypropylene, polyurethane and polysulfone) is recommended.