▼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 3rd, 5th, 7th and 14th infusions. In general, the MRI should be performed within approximately one week before the scheduled infusion of lecanemab and reviewed prior to proceeding with the infusion. 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	Nausea	Common

System Organ Class (SOC)	Adverse reaction	Frequency category
disorders		
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 HPRA Pharmacovigilance: www.hpra.ie

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
During the 18-month treatment period in Study 301, 3.4% (30/883) of patients treated with lecanemab 10 mg/kg every two weeks developed treatment-emergent anti-lecanemab antibodies, and 1.9% (17/885) developed neutralizing antibodies. The development of ADA had no impact on the pharmacokinetics, pharmacodynamics, efficacy, or safety of lecanemab.

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: 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

	Indicated Population	
Clinical Endpoints	**Lecanemab 10 mg/kg every 2 weeks**	**Placebo**
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

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8. MARKETING AUTHORISATION NUMBER

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Date of first authorisation: 15 April 2025

10. DATE OF REVISION OF THE TEXT

April 2026

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