LEQEMBI®▼ (lecanemab)

A Guide for Healthcare Professionals

Important Safety Information to Minimise the Risks of Amyloid Related Imaging Abnormalities and Intracerebral Haemorrhage

Please also consider the Prescriber's Checklist and the Summary of Product Characteristics of lecanemab available in https://sdi.sfda.gov.sa/

▼ Healthcare professionals are asked to report any 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. Information for reporting of suspected adverse reactions can be found at the end of this guidance.

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA

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Important safety information

This guide is intended to provide information about the risk and the management of amyloid related imaging abnormalities (ARIA) and risk of intracerebral haemorrhage (ICH) for patients receiving lecanemab. It is intended for prescribing physicians, radiologists and other healthcare professionals supervising the treatment with lecanemab.

For information particularly relevant for radiologists, please refer to the section titled 'Monitoring and managing ARIA'.

All patients receiving treatment with lecanemab and/or their caregivers must be given a Patient Card and the Patient Information Leaflet by their prescribing physician.

Prescribing doctors must inform patients about the risks of receiving lecanemab, required monitoring with MRI scans and signs or symptoms of ARIA. Patients must be encouraged to urgently report any new neurological symptoms to their prescribing physician, or if this is not possible, to any other physician, including their General Practitioner or an emergency doctor. Prescribing doctors should advise their patients to keep the Patient Card with them at all times and show it to any healthcare professional who may treat them.

To obtain copies of the Patient Card, please contact Eisai Safety and Pharmacovigilance department on Email: ME_Safety@eisai.net

Please carefully read the Summary of Product Characteristics (SmPC) of lecanemab.

Contents

What is Lecanemab?

Lecanemab is a recombinant humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody that selectively binds to soluble (protofibrils) and insoluble (fibrils) forms of amyloid beta (Aβ), which are a major component of Aβ plaques. The accumulation of Aβ plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Lecanemab has been shown to produce a reduction in brain amyloid.

Indication

Lecanemab 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.

Lecanemab 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, recognise and manage infusion-related reactions.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- 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)
- Treatment with lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy

What is ARIA?

ARIA, an acronym of Amyloid Related Imaging Abnormalities, is a consequence of the presence of amyloid in blood vessel walls known as CAA. The majority of patients who have Alzheimer's disease also show CAA during neuropathological examination, which can lead to spontaneous ARIA and is associated with an increased risk of intracerebral haemorrhage. Use of monoclonal antibodies directed against aggregated forms of Aβ, such as lecanemab, increases the risk of ARIA. Studies have suggested that ARIA may be caused by the disruption of blood vessels with CAA and that the risk is increased by the clearance of Aβ from these vessels, but other mechanisms have also been hypothesised.

ARIA can manifest in two distinct forms identifiable through MRI: ARIA with oedema or sulcal effusions (ARIA-E) and ARIA with haemosiderin deposition (ARIA-H), including microhaemorrhage and superficial siderosis. In addition, intracerebral haemorrhages >1 cm in diameter have occurred.

Patients who are homozygous *APOE ε4* carriers have a higher incidence of ARIA when treated with monoclonal antibodies directed against aggregated forms of Aβ, including lecanemab, compared to heterozygous *APOE ε4* carriers and non-carriers. Lecanemab is not indicated for use in patients who are homozygous *APOE ε4* carriers.

Symptoms of ARIA

ARIA typically occurs early in treatment and is usually asymptomatic and identified through routine surveillance MRI.

Symptomatic ARIA occurred in 2% (16/757) of patients on lecanemab who are *APOE ε4* non-carriers or heterozygotes (the indicated population) in the Phase 3 study (Study 301).

Symptoms include:

- Headache
- Confusion
- Nausea
- Visual changes
- Dizziness
- Gait difficulty
- Seizures
- Focal neurological deficits

Serious and life-threatening events, including seizures and status epilepticus, can rarely occur. Serious symptoms associated with ARIA that required hospitalisation were reported in 0.4% (3/757) of patients on lecanemab who are *APOE ε4* non-carriers or heterozygotes in Study 301.

Symptoms associated with ARIA usually resolve over time. In Study 301, clinical symptoms associated with ARIA resolved in 75% (12/16) of patients who are *APOE ε4* non-carriers or heterozygotes during the 18-month study period.

ARIA-E (vasogenic cerebral oedema and sulcal effusion)

In Study 301, ARIA-E was observed in 9% (67/757) of patients who are *APOE ε4* non-carriers or heterozygotes treated with 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.

- ARIA-E usually resolved regardless of radiographic severity. Resolution on MRI occurred in 64% (43/67) of patients by 12 weeks, 87% (58/67) by 17 weeks and in 100% (67/67) overall

ARIA-H (cerebral microhaemorrhage and superficial siderosis)

In Study 301, ARIA-H was observed in 13% (98/757) of patients who are *APOE ε4* non-carriers or heterozygotes treated with 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) on lecanemab and 0.1% (1/764) on placebo. There was no increase in isolated ARIA-H (i.e. ARIA-H in patients who did not also experience ARIA-E) for lecanemab compared with placebo.

- ARIA-H with lecanemab generally occurs in association with ARIA-E
- ARIA-H usually stabilises but can remain visible on subsequent imaging

Intracerebral haemorrhage >1 cm in diameter

Intracerebral haemorrhage >1 cm in diameter was reported in 0.5% (4/757) of patients who are *APOE ε4* non-carriers or heterozygotes in Study 301 after treatment with lecanemab compared to 0.1% (1/764) of patients on placebo.

- Intracerebral haemorrhage >1 cm in diameter occurs randomly throughout the course of treatment in both placebo and lecanemab treated patients

- Intracerebral haemorrhages >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 or thrombolytic agents to a patient already being treated with lecanemab
- Lecanemab should not be used in patients with pre-treatment MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema or other findings which are suggestive of CAA
- Caution should be exercised when considering the use of lecanemab in patients with factors that indicate an increased risk for intracerebral haemorrhage
- The presence of an *APOE ε4* allele is associated with CAA, which has an increased risk for intracerebral haemorrhage

Concomitant antithrombotic medication

- An increased risk of ARIA or intracerebral haemorrhage was not observed with antiplatelet use. The use of concomitant aspirin and other antiplatelet therapy is permitted
- Treatment with lecanemab should not be initiated in patients receiving ongoing anticoagulant therapy
- Intracerebral haemorrhages have been observed in patients taking both lecanemab and anticoagulants, and in patients receiving thrombolytic agents during lecanemab treatment
  - 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
  - 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 ischaemic 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

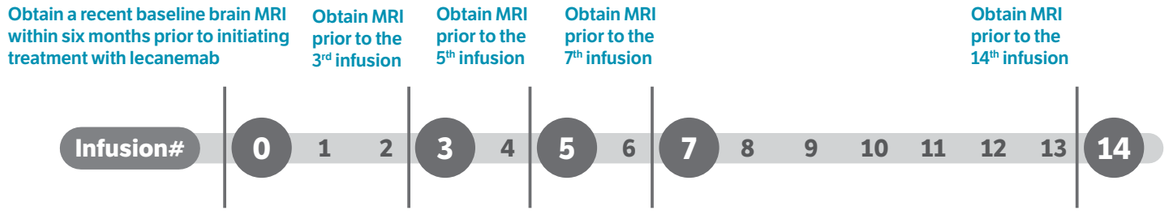
Monitoring and managing ARIA

Prior to treatment

- A recent baseline brain MRI (within 6 months) prior to treatment initiation with lecanemab is to be obtained to evaluate findings suggestive of CAA
- *APOE ε4* status should be investigated prior to initiation of treatment with lecanemab to inform the risk of developing ARIA
  - Prior to testing, patients should be appropriately counselled and consented according to national or local guidelines, as applicable
  - *APOE ε4* 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
  - The management recommendations for ARIA are the same whether an individual is an *APOE ε4* carrier or a non-carrier
- The presence of Aβ pathology must be confirmed via an appropriate test prior to initiating treatment

During treatment

- Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment
- If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI
- Regardless, MRI should be performed routinely during treatment, prior to the 3rd, 5th, 7th and 14th infusions. These scans should be performed using the same protocol as for the baseline MRI scans



Do NOT administer the 3rd, 5th, 7th, and 14th infusion until the MRIs have been reviewed."

ARIA radiographic severity grading

ARIA-E, ARIA-H microhaemorrhage, and ARIA-H superficial siderosis can be categorised by radiographic severity based on the following criteria:

ARIA type	Radiographic severity[1]		
ARIA-E	**Mild**	**Moderate**	**Severe**
	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.

Differential diagnosis

ARIA should be considered as the presumptive diagnosis when signal abnormalities on MRI are identified in patients recently exposed to monoclonal antibodies that remove amyloid plaque and in whom no evidence of any other inciting cause or underlying lesion can be found.

- In a suspected ARIA case, the full clinical picture must be taken into account before a diagnosis is confirmed
- MRI is key for the diagnosis and differential diagnosis of ARIA. Scanning at 3.0T is preferred and the use of 1.5T is endorsed as a minimum standard due to the limited availability of high field strength scanners
- The acquisition sequences to identify ARIA include T2* gradient echo (GRE) or susceptibility weight imaging (SWI) to detect ARIA-H and T2-weighted fluid attenuated inversion recovery (FLAIR) to detect ARIA-E
- Computed tomography (CT) would not be expected to detect milder forms of ARIA-E and is insensitive to the detection of ARIA-H
- Reliable diagnosis of ARIA may require specific training
- ARIA can present with focal neurological findings that mimic ischaemic stroke. MRI should be used to evaluate stroke-like symptoms in patients on lecanemab to distinguish ARIA from ischaemic stroke. In addition to acquisition sequences for ARIA, diffusion-weighted imaging (DWI) should be carried out to exclude an ischaemic stroke
  - ARIA-E is not associated with restricted diffusion, thus differentiating it from ischaemia
  - Signs and symptoms of ischaemic stroke, some of which may be seen with ARIA, may include: acute onset, hemiparesis, dysphasia or dysarthria, facial paresis, paraesthesia, eye movement abnormalities, and visual field defects

Recommendations for dosing interruptions or treatment discontinuation in patients with ARIA

Dosing recommendations for individuals with ARIA-E and ARIA-H are based on MRI severity of ARIA and presence of clinical symptoms.
Clinical symptom severity can be classified into:

- **Mild:** discomfort noticed, but no disruption of normal daily activity
- **Moderate:** discomfort sufficient to reduce or affect normal daily activity
- **Severe:** incapacitating, with inability to work or to perform normal daily activity

ARIA-E

- Dosing may continue in asymptomatic, radiographically mild ARIA-E cases
- For patients with asymptomatic radiographic findings of ARIA-E, enhanced clinical vigilance for symptoms of ARIA is recommended. Additional MRIs should be performed after 1 to 2 months to assess for resolution, or sooner if symptoms present
- Interrupt 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 judgement
- Use clinical judgement 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

ARIA-H

- Dosing may continue in asymptomatic, radiographically mild ARIA-H cases
- Interrupt dosing for any mild or moderate symptomatic 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
- In the event of radiographically severe or symptomatic severe ARIA-H, treatment with lecanemab should be permanently discontinued

Note to affiliates – please check the availability of relevant national guidance, appropriate use recommendations or national clinical practice on ARIA treatment and make a judgement call on the inclusion of these recommendations in the HCP guide.

Intracerebral haemorrhage

- Lecanemab should be permanently discontinued if intracerebral haemorrhage >1 cm in diameter occurs

Reporting of suspected adverse reactions

Please report any adverse event through the following:

National Pharmacovigilance Centre (NPC) at Saudi Food and Drug Authority (SFDA):
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

Eisai Kingdom of Saudi Arabia (EKS) – Safety and Pharmacovigilance department:
Jude Center, 4328 Salah Ad Din Al Ayyubi Rd,
4328, 8042, Riyadh
12233, building 3
Email: ME_Safety@eisai.net
Phone: +966 55 628 5221

Checklist for Prescribers of LEQEMBI®▼ (lecanemab)

▼ The prescribing healthcare professional must complete this checklist to confirm patient eligibility and ensure safe use of Lecanemab. Healthcare professionals are asked to report any suspected adverse reactions. Information on the reporting of adverse events can be found at the bottom of the last page of this document.

Patient's name: _____

Patient's medical record number: _____

Patient's date of birth: _____

Date: _____

LECANEMAB INDICATION

Lecanemab 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.

Lecanemab checklist before prescribing

This checklist is designed to support you in the appropriate initiation of lecanemab. Please note, if all responses to statements 1–7 are marked 'yes', the patient may be suitable for treatment with lecanemab.

PRIOR TO INITIAL TREATMENT:

1. The adult patient has a clinical diagnosis of mild cognitive impairment or mild dementia due to Alzheimer's disease with confirmed amyloid pathology — Yes ☐ No ☐

2. The patient is an *APOE ε4* non-carrier or heterozygote (understanding *APOE ε4* genotype is important to identify appropriate patients to treat) — Yes ☐ No ☐

3. A recent (within six months) baseline brain MRI has been obtained prior to initiating treatment with lecanemab — Yes ☐ No ☐

4. No findings were found on pre-treatment MRI that were suggestive of CAA (prior cerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema, or other findings) — Yes ☐ No ☐

5. The patient has no hypersensitivity to the active substance or to any of the excipients listed in Summary of Product Characteristics section 6.1 — Yes ☐ No ☐

6. If the patient has a bleeding disorder, it is under adequate control — Yes ☐ No ☐

7. The patient is not receiving ongoing anticoagulant therapy — Yes ☐ No ☐

8. *Precautions for use* – Consider the increased risk of intracerebral haemorrhage associated with the administration of anticoagulants and thrombolytics and the other risk factors listed in Summary of Product Characteristics section 4.4 — Yes ☐ No ☐

9. The patient has been given a patient information leaflet:

- Digital via QR code — Yes ☐ No ☐
- Handout (print version) — Yes ☐ No ☐

10. The patient has been given and completed the Patient Card and has been informed to keep it with them and to give it to any consulting physicians — Yes ☐ No ☐

11. Have you verbally informed patients and caregivers of the information provided in the Patient Card, risks of lecanemab, MRI scans, signs or symptoms of adverse reactions and when to seek attention from a healthcare professional? — Yes ☐ No ☐

12. Has the patient been booked in for the following MRI scans?

- MRI prior to 3rd infusion — Yes ☐ No ☐
- MRI prior to 5th infusion — Yes ☐ No ☐
- MRI prior to 7th infusion — Yes ☐ No ☐
- MRI prior to 14th infusion

Additional Patient Cards can be ordered from Eisai Safety and Pharmacovigilance department on Email: ME_Safety@eisai.net.

The lecanemab Summary of Product Characteristics and Patient Information Leaflet are available in https://sdi.sfda.gov.sa/

Reporting of suspected adverse reactions

Please report any adverse event through the following:

National Pharmacovigilance Centre (NPC) at Saudi Food and Drug Authority (SFDA):
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

Eisai Kingdom of Saudi Arabia (EKS) – Safety and Pharmacovigilance department:
Jude Center, 4328 Salah Ad Din Al Ayyubi Rd,
4328, 8042, Riyadh
12233, building 3
Email: ME_Safety@eisai.net
Phone: +966 55 628 5221

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