Important Safety Information to Minimize the Risks of Amyloid Related Imaging Abnormalities

A Guide for Healthcare Professionals

Please also consider the prescribing information of Leqembi as approved by the Israeli MOH

LEQEMBI™
(lecanemab)

Important safety information

This guide is intended to provide information for prescribers, radiologists and other treating healthcare professionals about the risk and the management of Amyloid Related Imaging Abnormalities (ARIA) for patients with early Alzheimer's disease receiving LEQEMBI.

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

All patients receiving treatment with LEQEMBI must be given a Guidance for Patients & Caregivers brochure by their prescribing physician to inform them about the symptoms of ARIA. These symptoms must be urgently reported to their prescribing physician, or if this is not possible, to any other physician, including their General Practitioner or an emergency doctor.

To obtain copies of the Guidance for Patients & Caregivers brochure, please contact by email: revital_givoni@eisai.net or download via https://eisaipro.eu/en-il.

For more information, please refer to the prescribing information of LEQEMBI as approved by the Israeli MOH at: israeldrugs.health.gov.il

All patients receiving treatment with LEQEMBI must be given a Guidance for Patients & Caregivers brochure.

Content

What is LEQEMBI?

LEQEMBI is a recombinant humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta (Aβ).

Indication

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

The presence of Aβ pathology must be confirmed using approved methods such as amyloid Positron Emission Tomography (PET) scan or Cerebrospinal Fluid (CSF) analysis or equivalent validated methods, prior to initiating treatment.

Contraindications

LEQEMBI is contraindicated in patients with hypersensitivity to lecanemab or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis.

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 cerebral amyloid angiopathy (CAA). Neuroimaging findings that may indicate CAA include evidence of prior intracerebral hemorrhage, cerebral microhemorrhage, and cortical superficial siderosis. The presence of an ApoE ε4 allele is also associated with 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 amyloid beta, such as LEQEMBI, 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 amyloid beta from these vessels, but other mechanisms have also been hypothesised.

ARIA can manifest in three distinct forms identifiable through Magnetic Resonance Imaging (MRI): ARIA with edema or sulcal effusions (ARIA-E); ARIA with haemosiderin deposition (ARIA-H), involving microhaemorrhage or superficial siderosis; and intracerebral haemorrhage >1 cm in diameter.

What is ARIA? (Continued)

Symptoms of ARIA

Symptomatic ARIA occurred in 3% (29/898) of patients treated with LEQEMBI in Clarity AD study.

Symptoms include:

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

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, can rarely occur. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI.

Symptoms associated with ARIA usually resolve over time. In Clarity AD study, clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation.

ARIA-E (vasogenic cerebral edema)

In Clarity AD study, ARIA-E was observed in 13% (113/898) of patients treated with LEQEMBI compared with 2% (15/897) of placebo patients. ARIA-E is usually asymptomatic, with symptomatic ARIA-E reported in 3% of patients.

- The incidence of symptomatic ARIA-E is higher in APOE ε4 homozygous carriers than APOE ε4 heterozygous carriers and APOE ε4 non-carriers. However, once ARIA-E has occurred, the clinical course remains unchanged.
- ARIA-E usually resolves spontaneously regardless of radiographic severity.

ARIA-H (cerebral microhaemorrhage and superficial siderosis)

In Clarity AD study, ARIA-H was observed in 17% (152/898) of patients treated with LEQEMBI compared with 9% (80/897) of patients on placebo. ARIA-H is usually asymptomatic.

There was no increase in isolated ARIA-H (i.e. ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI compared to placebo.

- The incidence of isolated ARIA-H is higher in APOE ε4 homozygous carriers than APOE ε4 heterozygous carriers and APOE ε4 non-carriers.
- ARIA-H generally occurs in association with an occurrence of ARIA-E.

What is ARIA? (Continued)

Intracerebral haemorrhage >1 cm in diameter

Intracerebral haemorrhage >1 cm in diameter was reported in 0.7% (6/898) of patients in Clarity AD study after treatment with LEQEMBI compared to 0.1% (1/897) patients on placebo.

- Signs suggestive of CAA on screening MRI (prior cerebral haemorrhage greater than 1 cm in greatest diameter, more than 4 microhaemorrhages, superficial siderosis, vasogenic edema) or other lesions like aneurysms or vascular malformations can potentially increase the risk of intracerebral haemorrhage.
- The presence of APOE ε4 allele is associated with CAA, which has an increased risk for intracerebral haemorrhage >1 cm in diameter.
- Fatal cerebral haemorrhage has occurred in a patient taking an anti-amyloid monoclonal antibody in the setting of focal neurologic symptoms of ARIA and the use of a thrombolytic agent. Caution should be exercised when considering the use of LEQEMBI in patients with factors that indicate an increased risk for intracerebral haemorrhage and administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator).

Concomitant antithrombotic medication

Baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed in Clarity AD study if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Antiplatelet agents were used in the trial with no apparent increase in the risk of ARIA-E, ARIA-H or intracerebral haemorrhage with LEQEMBI.

Intracerebral haemorrhages >1 cm in diameter have been observed in patients taking both LEQEMBI and anticoagulants and in patients receiving thrombolytic agents during LEQEMBI 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 LEQEMBI:

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

Treatment with LEQEMBI should be initiated with caution in patients receiving ongoing anticoagulant therapy.

For incidence of ARIA please refer to Section 6 'ADVERSE REACTIONS' of the prescribing information of LEQEMBI.

Monitoring and Managing ARIA

Prior to treatment

- A recent baseline brain MRI should be obtained prior to treatment initiation with LEQEMBI.
- Testing for APOE ε4 status should be performed prior to initiation of treatment with LEQEMBI to inform the risk of developing ARIA.

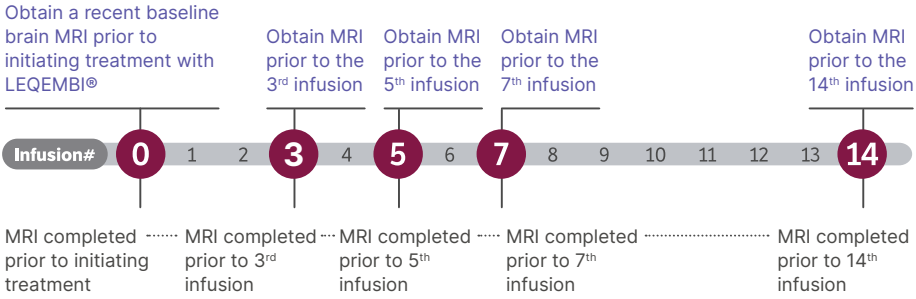
If testing is not conducted, the patient can still receive treatment with LEQEMBI; however, it will remain uncertain whether they carry the APOE ε4 gene and are at a heightened risk for ARIA.

The risk of ARIA across genotypes and the implications of genetic testing results should be discussed with patients prior to testing.

The management recommendations for ARIA remain consistent whether an individual is an APOE ε4 carrier or a noncarrier.

During treatment

- Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment.
- An MRI should be performed periodically during the course of treatment: prior to the 3rd, 5th, 7th and 14th infusions.



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

- In general, the MRI should be performed within approximately one week before the scheduled infusion of LEQEMBI and reviewed prior to proceeding with the infusion.
- If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.
- Inform patients that some symptoms of ARIA-E can mimic ischemic stroke. Advise patients to inform their healthcare providers that they are being treated with LEQEMBI.
- If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

ARIA radiographic severity grading

The management of patients with ARIA-E and ARIA-H depends on clinical symptoms and radiographic severity.

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]		
	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. LEQEMBI SPC as approved by the Israeli MOH.

Differential diagnosis

ARIA-E should be considered as the presumptive diagnosis when the radiographic signal abnormalities on MRI described above 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.[2]
- The acquisition sequences to identify ARIA include T2* GRE (gradient recalled echo) or SWI (susceptibility weighted imaging) to detect ARIA-H and T2-FLAIR to detect ARIA-E.[2]
- Computerized 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.

2. Cogswell PM, et al. AJNR Am J Neuroradiol. 2022;43(9):E19–E35

ARIA radiographic severity grading
(Continued)

Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, 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 LEQEMBI.

Dosing recommendations for patients with ARIA

Dosing recommendations for individuals with ARIA-E and ARIA-H are based on MRI severity 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

Dosing recommendations for patients with ARIA-E

Clinical symptom Severity	ARIA-E severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing	Suspend dosing
Mild	May continue dosing based on clinical judgment		
Moderate or Severe	Suspend dosing		

Dosing may continue in asymptomatic, mild radiographic ARIA-E cases. In cases that are both mildly symptomatic and radiographically mild, dosing may continue based on clinical judgement. Suspend dosing for any moderate or severe symptomatic or radiographically ARIA-E. A follow-up MRI to assess for radiographic resolution 2 to 4 months after initial identification should be performed. Once the MRI demonstrates radiographic resolution and symptoms, if present and resolve, resumption of dosing should be guided by clinical judgment.

Dosing recommendations for patients with ARIA-H

Clinical symptom Severity	ARIA-H severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing	Suspend dosing
Symptomatic	Suspend dosing		

ARIA radiographic severity grading
(Continued)

In case of mild or moderate symptomatic or moderate asymptomatic ARIA-H, dosing should be suspended until MRI demonstrates radiographic stabilisation and symptoms, if present, resolve. Resumption of dosing should be guided by clinical judgment and a follow-up MRI should be considered to assess for stabilisation 2 to 4 months after initial identification.

In case of severe ARIA-H, dosing should be suspended until MRI demonstrates radiographic stabilisation and symptoms, if present, resolve. Clinical judgement should be used to consider whether to continue treatment or permanently discontinue LEQEMBI.

Dosing recommendations for patients with intracerebral haemorrhage >1 cm in diameter

In patients who develop intracerebral haemorrhage >1 cm in diameter during treatment with LEQEMBI, suspend dosing until MRI demonstrates radiographic stabilisation and symptoms, if present, resolve. Use clinical judgment in considering whether to continue treatment after radiographic stabilisation and resolution of symptoms or permanently discontinue treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il or emailed the registration holder's safety unit at: eir_pv@eisai.net

For full information please refer to LEQEMBI SPC as approved by the Israeli MOH.

Notes

Eisai

This guide, format and content have been approved by the IMOH in September 2025, version no. 02

IL-LECA-25-00034