

KISUNLA[®] ▼ (donanemab)

A Guide for Healthcare Professionals

Important Safety Information to Minimise the Risks of Amyloid-Related Imaging Abnormalities

▼ 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.

Adverse events and product complaints should be reported. Reporting forms and information can be found on the HPRA website: www.hpra.ie. Adverse events and product complaints should also be reported to Lilly: please call Lilly Ireland on 01 664 0446.

This document contains important information to assist the initial discussion with your patients when prescribing donanemab and when monitoring treatment. It should be read in conjunction with the Summary of Product Characteristics (SmPC). The educational material contains a guide for healthcare professionals and a prescriber checklist.

Important safety information

This guide is intended to provide information for healthcare professionals (HCPs), including prescribers and radiologists, about the risk and the management of amyloid-related imaging abnormalities (ARIA) and intracerebral haemorrhage for patients with early symptomatic Alzheimer's disease (AD) receiving Kisunla (donanemab) treatment.

For information particularly relevant for prescribers before and during treatment, please refer to the section titled 'Prescriber Checklist'.

All patients receiving treatment with donanemab must be given a Patient Card and the Patient Information Leaflet by their prescribing physician and counselled about the risk of developing ARIA and the symptoms of which to be aware. Patients must be informed 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/caregivers to keep the Patient Card with them at all times and provide to HCP in emergency situations.

To obtain further copies of the Guide for Healthcare Professionals or the Patient Card, please contact the Eli Lilly Medical Information department (UKMedInfo@Lilly.com or TEL: 01 664 0446, choosing option 1 for Medical Information) or a Lilly representative/medical science liaison.

Please carefully read the Summary of Product Characteristics (SmPC) for donanemab at [medicines.ie](https://www.medicines.ie)

Electronic copies of this guide and the Patient Card can be found at [medicines.ie](https://www.medicines.ie)

CONTROLLED ACCESS PROGRAMME

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

Donanemab treatment should be administered under the supervision of a multidisciplinary team trained in monitoring and management of ARIA and experienced in detecting and managing infusion related reactions to ensure adequate management of patients treated with donanemab.

The CAP allows for pre-selection of centres with required criteria, including:

- a multidisciplinary team able to assess eligibility for donanemab
- access to a validated method to assess brain amyloid pathology
- access to apolipoprotein E ϵ 4 (ApoE ϵ 4) tests
- access to intravenous infusions
- access to magnetic resonance imaging (MRI) in a scheduled and non-scheduled way to monitor for ARIA, and
- access to educational materials.

This will be followed by drug distribution to pharmacies of these selected centres with affiliated prescribers, who have received HCP educational materials on donanemab treatment. Prescribers within these centres will, prior to a patient receiving donanemab, use the registration system to

- attest to receiving and understanding the required HCP education guide
- confirm that the (anonymised) patient meets required eligibility criteria per label
- and verify that the patient has been counselled regarding the risks of donanemab and provided the patient card.

The CAP can be accessed through this link: <https://alzheimers.lilly.com/>

The Kisunla Unique Identifier should be noted for the patient in the medical record for the first infusion and will be required when placing an order for donanemab. Without this information, the patient should not receive their first infusion with donanemab.

For further information, please contact UKMedInfo@lilly.com

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What is Donanemab¹

Donanemab is an immunoglobulin gamma 1 monoclonal antibody with high affinity for a modified, N-terminal truncated form of amyloid beta (N3pE A β). N3pE A β is present in brain amyloid plaques at low levels and not detected in plasma and cerebrospinal fluid. Donanemab binds to N3pE A β and aids plaque removal through microglial-mediated phagocytosis.

Indication¹

Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to AD (early symptomatic AD) who are ApoE ϵ 4 heterozygotes or non-carriers with confirmed amyloid pathology (see Section 4.4 of SmPC).

The testing for ApoE ϵ 4 carrier status is mandatory prior to initiating donanemab treatment to inform the risk of developing ARIA (see Sections 4.1, 4.2, and 4.4 of SmPC). Prior to testing, patients should be appropriately counselled and consented according to national or local guidelines, as applicable.

Contraindications¹

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the Kisunla SmPC.
- Baseline MRI findings of prior intracerebral haemorrhage, more than 4 microhaemorrhages, superficial siderosis or vasogenic oedema (ARIA-E), or other findings, which are suggestive of cerebral amyloid angiopathy (CAA) (see Section 4.4 of SmPC).
- Patients with bleeding disorders that are not under adequate control.
- Initiation in patients receiving ongoing anticoagulant therapy (see Section 4.4 of SmPC).
- Severe white matter disease (see Section 4.4 of SmPC).
- Patients with poorly controlled hypertension.
- Conditions that do not allow MRI assessment, including claustrophobia or the presence of metal (ferromagnetic) implants/cardiac pacemaker.

What is ARIA¹⁻⁶

ARIA, an acronym for Amyloid-Related Imaging Abnormalities, is a consequence of the presence of amyloid in blood vessel walls, known as CAA.² The majority of patients who have AD also show CAA during neuropathological examination, which can lead to spontaneous ARIA and is associated with an increased risk of intracerebral haemorrhage.^{3,4} Use of monoclonal antibodies directed against aggregated forms of amyloid beta, such as donanemab, 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.^{3,5}

ARIA can manifest in 2 distinct forms identifiable through MRI: ARIA with brain oedema or sulcal effusions (ARIA-E) and ARIA with haemorrhage or haemosiderin deposition (ARIA-H), including microhaemorrhage and superficial siderosis.^{2,6} In addition to ARIA, intracerebral haemorrhages greater than 1 cm in diameter have occurred in patients treated with this class of medications, including donanemab.¹

Most ARIA reactions occur within 24 weeks of initiation of treatment, with most serious ARIA reactions occurring within 12 weeks of initiation of treatment.¹

Risk factors of ARIA^{2,6}

- ApoE ε4 carrier status (homozygotes greater than heterozygotes) compared with noncarriers
- pretreatment cerebral microhaemorrhage, and
- superficial siderosis on MRI.

Symptoms of ARIA¹

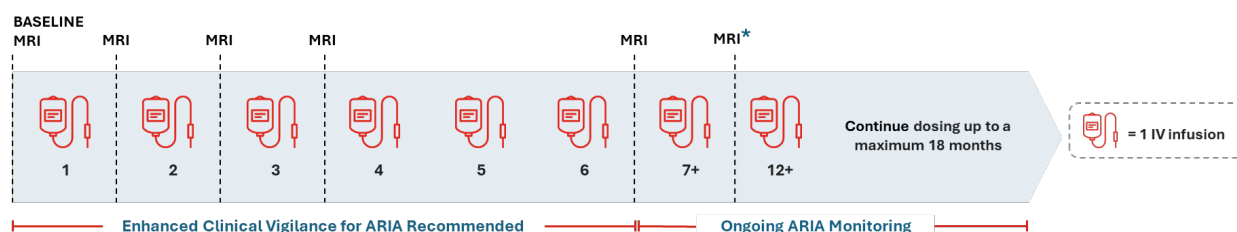
Donanemab use may cause ARIA-E or ARIA-H, which is usually asymptomatic. Patients should be instructed to seek medical advice immediately if signs or symptoms suggesting ARIA appear. These include, but are not limited to,

- | | | |
|----------------|-------------|--------------------------------|
| • headache | • tremor | • alteration of consciousness |
| • nausea | • dizziness | • speech disturbances |
| • vomiting | • confusion | • worsening cognitive function |
| • unsteadiness | • seizures | • visual disturbances |

Symptoms of ARIA may mimic stroke or stroke-like symptoms.

MRI monitoring for ARIA¹

An MRI should be performed at baseline (within 6 months prior to initiating treatment), prior to the second dose, prior to the third dose, prior to the fourth dose, and prior to the seventh dose. An additional MRI at 1 year of treatment (prior to the twelfth dose) in patients with ARIA risk factors, such as ApoE ϵ 4 heterozygotes, and patients with previous ARIA events earlier in treatment, should be performed. Additional MRI is indicated if ARIA symptoms occur.



Abbreviations: ApoE ϵ 4 = apolipoprotein E ϵ 4; ARIA = amyloid-related imaging abnormalities; IV = intravenous; MRI = magnetic resonance imaging.

*Additional MRI prior to 12th dose is performed in patients with ARIA risk factors, such as ApoE ϵ 4 heterozygotes, and patients with previous ARIA events earlier in treatment.

ARIA radiographic severity grading¹

ARIA-E and ARIA-H can both be classified as mild, moderate, or severe based on MRI, and as symptomatic or asymptomatic based upon the clinical symptoms.

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted
ARIA-H microhaemorrhage	≤4 new incident microhaemorrhages	5 to 9 new incident microhemorrhages	≥10 new incident microhaemorrhages
ARIA-H superficial siderosis	1 new or increased focal area of superficial siderosis	2 new or increased focal areas of superficial siderosis	>2 new or increased focal areas of superficial siderosis

Abbreviations: ARIA-E = amyloid-related imaging abnormalities-oedema/effusions; ARIA-H = amyloid-related imaging abnormalities haemorrhage/haemosiderin deposition; FLAIR = fluid-attenuated inversion recovery.

Dosing interruption and treatment discontinuation for patients with ARIA¹

The recommendations for dosing interruptions or treatment discontinuation for patients with ARIA-E and ARIA-H are based on MRI severity and presence of clinical symptoms.

Clinical Symptom	ARIA-E and ARIA-H Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	Consider suspending dosing	Suspend dosing	Discontinue dosing
Symptomatic	Suspend dosing	Suspend dosing	Discontinue dosing

Abbreviations: ARIA-E = amyloid-related imaging abnormalities-oedema/effusions;
ARIA-H = amyloid-related imaging abnormalities haemorrhage/haemosiderin deposition;
MRI = magnetic resonance imaging.

A follow-up MRI to assess for resolution (ARIA-E) or stabilisation (ARIA-H) should be performed 2 to 4 months after initial identification. Resumption of dosing or permanent discontinuation after ARIA-E resolution and ARIA-H stabilisation should be guided by clinical judgement, including re-evaluation of risk factors. Standard supportive treatment, including corticosteroids, may be considered in case of ARIA-E.

In the event of radiographically or symptomatic severe ARIA-E or ARIA-H, treatment with donanemab should be permanently discontinued.

Donanemab should also be permanently discontinued after clinically serious ARIA-E, serious ARIA-H, or intracerebral haemorrhage greater than 1 cm.

Use clinical judgement in considering whether to continue dosing in patients with recurrent ARIA. Treatment with donanemab should be discontinued following recurrent symptomatic or radiographically moderate or severe ARIA events.

Concomitant antithrombotic medication¹

Events of ARIA-H and intracerebral haemorrhage greater than 1 cm have been reported in patients receiving antithrombotic agents during donanemab treatment. Thus, additional caution should be exercised when considering the administration of antithrombotic or a thrombolytic agent (for example, tissue plasminogen activator) to a patient already being treated with donanemab:

- If anticoagulation needs to be commenced during therapy with donanemab (for example, incident arterial thromboses, acute pulmonary embolism, or other life-threatening indications), then donanemab should be paused. Donanemab can be reinstated if anticoagulation is no longer medically indicated. The use of concomitant aspirin and other antiplatelet therapy is permitted.
- Although there was only limited exposure to thrombolytic agents in the clinical trials, there is a plausible risk of severe intracranial haemorrhage resulting from

concomitant use with thrombolytics. Use of thrombolytic agents should be avoided except for immediately life-threatening indications with no alternative management (for example, pulmonary embolism with haemodynamic compromise) when the benefits could outweigh the risks.

ARIA should be considered in the differential diagnosis of patients presenting with stroke-like symptoms.

ARIA can cause focal neurologic deficits that can mimic an ischaemic stroke. Clinicians treating ischaemic stroke should consider whether such symptoms could be due to ARIA before giving thrombolytic therapy to a patient being treated with donanemab. MRI or identification of vascular occlusion can help identify that ischaemic stroke rather than ARIA is the aetiology and inform the use of thrombolytics or thrombectomy when appropriate.

Treatment with donanemab must not be initiated in patients receiving ongoing anticoagulant therapy (see Section 4.3 of SmPC).

Checklist for Prescribers of Kisunla®▼ (donanemab)¹

Please acknowledge and confirm that the following considerations are/will be adhered to

A. Prior to initiating treatment with donanemab		
	Yes	No
1. Has the initiation of donanemab treatment in the patient been captured in the 'CAP Registration System' implemented as part of the controlled access programme?	☐	☐
2. Is the patient an APOE ε4 non-carrier or heterozygote and do you understand that APOE ε4 carrier status testing is mandatory to inform the risk of developing ARIA? <i>The use of donanemab in ApoE ε4 homozygous carrier patients is not indicated (see Section 4.1 of SmPC).</i>	☐	☐
3. Has the patient been given the Patient Card and been informed about the risks of this medicinal product?	☐	☐
4. Has the presence of amyloid beta pathology and a clinical diagnosis of either mild cognitive impairment due to AD or mild AD dementia been confirmed?	☐	☐
5. Has an MRI been performed at baseline (within 6 months prior to initiating treatment) for risk factors of ARIA, including presence of cerebral microhaemorrhage and superficial siderosis? <i>The use of donanemab in patients with >4 microhaemorrhages or superficial siderosis is contraindicated.</i>	☐	☐
6. Can you confirm that the patient does not present any of the contraindications described in Section 4.3 of the SmPC?	☐	☐
B. Monitoring during treatment		
	Yes	No
1. The treatment will be maintained until amyloid plaques are cleared (for example, at 6 or 12 months, see Section 5.1 of SmPC) as confirmed using a validated method, and the maximum treatment duration will be 18 months, which will not be exceeded even if plaque clearance is not confirmed.	☐	☐

	Yes	No
2. The patient has been booked in for the following MRI scans:		
MRI prior to the second dose	☐	☐
MRI prior to the third dose	☐	☐
MRI prior to the fourth dose	☐	☐
MRI prior to the seventh dose	☐	☐
MRI prior to the twelfth dose if the patient has ARIA risk factors, such as ApoE ε4 heterozygotes	☐	☐
3. In the event of ARIA occurring earlier in the treatment, please confirm that an additional MRI at 1 year of treatment (prior to the twelfth dose) will be performed*	☐	☐

***In case of ARIA, please follow the recommendations for dosing interruptions described in section 4.2 of the SmPC. Additional MRI is indicated if ARIA symptoms occur. A follow-up MRI to assess for resolution (ARIA-E) or stabilisation (ARIA-H) should be performed 2 to 4 months after initial identification.**

Standard supportive treatment, including corticosteroids, may be considered in case of ARIA-E.

Resumption of dosing or permanent discontinuation after ARIA-E resolution and ARIA-H stabilisation should be guided by clinical judgement, including re-evaluation of risk factors.

Donanemab should be permanently discontinued after serious ARIA-E, serious ARIA-H, intracerebral haemorrhage greater than 1 cm, or recurrent symptomatic or radiographically moderate or severe ARIA events.

References

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