# KISUNLA®▼(DONANEMAB)
# A GUIDE FOR HEALTHCARE PROFESSIONALS

## IMPORTANT SAFETY INFORMATION ON DONANEMAB TREATMENT TO MINIMISE RISK OF AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA) AND INTRACEREBRAL HAEMORRHAGE (ICH)

▼ 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.

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. You can report via:

- the Yellow Card website www.mhra.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report suspected adverse drug reactions to the Yellow Card scheme by calling **0800 731 6789** for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible. By reporting adverse drug reactions, you can help provide more information on the safety of this medicine.

Adverse events and product complaints should also be reported to Lilly: please call Lilly UK on **01256 315 000**

This HCP Guide fulfils the conditions of the marketing authorisation

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# IMPORTANT SAFETY INFORMATION

This guide is intended to provide information for healthcare professionals, including prescribers and radiologists, about the risk and management of amyloid-related imaging abnormalities (ARIA) and intracerebral haemorrhage (ICH) in patients with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD) receiving donanemab.

## PATIENT ALERT CARD

Patients who are prescribed donanemab **must be provided with a Patient Alert Card** and a copy of the **Patient Information Leaflet** before they start treatment. The materials include key information about the **patient's treatment,** the **signs and symptoms of ARIA/ICH** and their **emergency contacts** to be shared with other healthcare professionals involved in their medical care.

Patients must be informed that they need to **urgently report new neurological symptoms** to a physician and to **always keep the patient alert card on them** and show it to any healthcare professional who may treat them.

An optional patient bracelet may also be offered to patients receiving donanemab. This bracelet contains a QR code and a link to a webpage providing only basic information on the risk of ARIAs associated with donanemab. The information provided is not required under the terms of the product licence; therefore, the bracelet has not been reviewed or approved by the MHRA.

To obtain copies of the Patient Alert Card, please contact the Lilly Medical Information department (UKMedInfo@Lilly.com or TEL: 01256 315000) or a Lilly representative/Medical Science Liaison.

Please carefully read the Summary of Product Characteristics for donanemab at: https://www.medicines.org.uk/emc/product/16014/smpc#gref

Electronic copies of this guide and the Patient Alert Card can be found on www.medicines.org.uk

## CONTROLLED ACCESS PROGRAMME (CAP)

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 a CAP.

The CAP can be accessed through this link: alzheimers.uk.lilly.com/register

The Kisunla Unique Identifier should be noted for the patient in the Medical Record for the first infusion. Without this information, the patient should not receive their first infusion with donanemab.

For further information please contact UKMedInfo@Lilly.com

# WHAT IS DONANEMAB?

Donanemab is an immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble, modified, N-terminal truncated form of amyloid beta (N3pG Aβ) present only in brain amyloid plaques. Donanemab binds to N3pG Aβ and aids plaque removal through microglial-mediated phagocytosis. Donanemab has been shown to reduce brain amyloid levels and slow cognitive and functional decline.

## INDICATION

**Donanemab is indicated for the treatment of MCI and mild dementia due to AD in adult patients that are apolipoprotein E ε4 (APOE ε4) heterozygotes or non-carriers.**

Donanemab is not indicated for use in patients who are APOE ε4 homozygotes, as the benefit-risk ratio is negative in this patient subgroup.

The presence of Aβ pathology should be confirmed prior to initiating donanemab treatment using a validated test such as amyloid Positron Emission Tomography (PET) scan or cerebrospinal fluid (CSF) analysis, or equivalent validated methods.

Treatment should be continued until amyloid plaques are cleared as confirmed using a validated method up to a maximum of 18 months. Treatment should be continued for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible.

Testing for APOE ε4 status should be performed prior to initiation of treatment. Prior to testing, patients should be appropriately counselled and consented according to national or local guidelines, as applicable.

## CONTRAINDICATIONS

- Pre-treatment magnetic resonance imaging (MRI) findings suggestive of cerebral amyloid angiopathy (CAA) that increase the risk of ARIA or ICH:
  - Acute or subacute cerebral haemorrhage
  - Superficial siderosis
  - More than 4 microhaemorrhages (defined as ≤1 cm in diameter on the T2* sequence)
  - Severe white matter disease
  - ARIA oedema/effusions (ARIA-E)
  - Previous cerebral haemorrhage (defined as >1 cm diameter in the T2* sequence) or previous subarachnoid haemorrhage unless it is no longer at risk of re-bleeding
- Any finding that could prevent a satisfactory MRI evaluation for safety monitoring
- Treatment with donanemab should not be initiated in patients receiving ongoing anticoagulant therapy

# WHAT IS ARIA?

ARIA can occur as a result of amyloid in blood vessel walls, referred to as CAA. CAA is prevalent in patients with AD, including untreated patients. CAA can cause spontaneous ARIA-E / ARIA haemorrhage/haemosiderin (ARIA-H) and is associated with an increased risk of ICH. Monoclonal antibodies directed against Aβ, including donanemab, can cause ARIA. This may be a result of Aβ removal in treated patients leading to a greater risk of disruption to blood vessels with CAA, though other mechanisms have also been proposed.

The safety and efficacy of use in patients with a higher prevalence of CAA e.g. Down syndrome and autosomal dominant AD is unknown.

ARIA are usually asymptomatic, detectable on routine MRI imaging, and mild-to-moderate in severity. ARIA can be categorised as ARIA-E or ARIA-H following MRI detection. Most serious ARIA events occurred within 12 weeks of initiation of treatment with donanemab, and an additional MRI prior to the third dose may aid in earlier detection of ARIA. Serious and life-threatening cases of ARIA have been observed and some have been fatal. Serious ICH >1 cm, some of which has been fatal, has occurred in patients treated with donanemab. 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 in a patient being treated with donanemab.

APOE ε4 carriers have a higher frequency (homozygotes greater than heterozygotes) of ARIA-E and ARIA-H compared to noncarriers. **Donanemab is not indicated for use in patients who are APOE ε4 homozygotes**. Testing for APOE ε4 status should be performed prior to initiation of treatment. Prior to testing, patients should be appropriately counselled and consented according to national or local guidelines, as applicable.

In the TRAILBLAZER-ALZ and TRAILBLAZER-ALZ 2 placebo-controlled studies in patients with AD, a total of 984 adult patients received at least one dose of donanemab. Of these, based on the APOE ε4 carrier status, 30% (291/984) were noncarriers, 53% (522/984) were heterozygotes and 17% (168/984) were homozygotes.

| APOE ε4 Status | Non-carriers | Heterozygotes | Homozygotes |
|---|---|---|---|
| Incidence of ARIA[a] | 24.1% (n=70/291) | 37.4% (n=195/522) | 58.3% (n= 98/168) |
| Incidence of symptomatic ARIA-E[a] | 4.1% (n=12/291) | 6.1% (n=32/522) | 7.7% (n= 13/168) |
| Incidence of symptomatic ARIA-H[b] | 0.3% (n=1/291) | 1.3% (n=7/522) | 1.2% (n=2/168) |
| Incidence of serious ARIA events[a] | 0.7% (n=2/291) | 1.7% (n=9/522) | 3% (n= 5/168) |

[a]Kisunla® Summary of Product Characteristics.

[b]Data on file. Lilly UK.

**Donanemab is not indicated for use in patients who are APOE ε4 homozygotes**.

Among the patients who experienced an event of ARIA-E and continued on donanemab with or without dose interruption, the rates of recurrence were 32.4% (11/34) in non-carriers, 26.7% (27/101) in heterozygous carriers, and 28.6% (14/49) in homozygous carriers.

Among the patients who experienced an event of ARIA-H and continued on donanemab with or without dose interruption, the rates of recurrence were 35.1% (13/37) in non-carriers, 39.1% (45/115) in heterozygous carriers, and 51.7% (31/60) in homozygous carriers.

## SYMPTOMS OF ARIA

**The following ARIA incidence data include clinical trial results for the indicated population only, excluding data from homozygote patients for whom donanemab is not indicated.**

Symptomatic ARIA occurred in 5.8% (47/816) of patients treated with donanemab. Serious ARIA events were reported in 1.3% (11/816) of patients treated with donanemab. Clinical symptoms associated with ARIA-E resolved in 75% (33/44) of patients.

Symptoms of ARIA may include, but are not limited to:

- Headache
- Confusion
- Nausea
- Vomiting
- Unsteadiness
- Dizziness
- Tremor
- Visual disturbances
- Speech disturbances
- Worsening cognitive function
- Alteration of consciousness
- Seizures
- Focal neurological deficits

The majority of first ARIA radiographic events in the placebo-controlled studies occurred early in treatment (within 24 weeks of initiation of treatment), although ARIA can occur at any time and patients can have more than one episode. Patients must be instructed to seek **urgent medical attention** if they develop any features of ARIAs.

### ARIA-E (vasogenic oedema and sulcal effusions)

ARIA-E was observed in 20.8% (170/816) of patients treated with donanemab compared with 1.6% (13/825) of patients on placebo.

- The maximum radiographic severity for ARIA-E was mild in 6.5% of patients, moderate in 12.3% of patients, and severe in 1.7% of patients
- The majority of ARIA-E was asymptomatic with symptomatic ARIA-E reported for 5.4% of patients treated with donanemab in placebo controlled clinical trials
- The median time to resolution of ARIA-E was approximately 9 weeks

## ARIA-H (cerebral microhaemorrhage and superficial siderosis)

ARIA-H usually occurs with ARIA-E; however, ARIA-H can occur spontaneously in patients with AD, independent of treatment. ARIA-H was observed in 26.7% (218/816) of patients treated with donanemab compared with 11.6% (96/825) of patients on placebo.

- The maximum radiographic severity for ARIA-H was mild in 14.1% of patients, moderate in 5.0% of patients, and severe in 7.5% of patients
- The majority of ARIA-H was asymptomatic, with symptomatic ARIA-H reported for 1.0% (8/816) of patients treated with donanemab compared with 0.2% (2/825) of patients on placebo
- ARIA-H does not resolve radiographically; stabilisation was defined as no new/increased superficial siderosis and not more than 1 new microhaemorrhage on subsequent MRI
- Isolated ARIA-H (ie, ARIA-H in patients who did not also experience ARIA-E) was observed in 11.8% (96/816) of donanemab treated patients compared to 11% (91/825) on placebo

## INTRACEREBRAL HAEMORRHAGE >1 CM

ICH >1 cm in diameter was reported in 0.4% (3/816) of patients after treatment with donanemab compared to 0.2% (2/825) of placebo-treated patients. Fatal events of ICH in patients taking donanemab have been observed.

Patients should be monitored for indicators of ICH throughout donanemab treatment.

The presence of an APOE ε4 allele is associated with CAA, which has an increased risk of ICH. The number of events and the limited exposure to other non-acetylsalicylic acid antithrombotic medicines limit definitive conclusions about the risk of ARIA or intracerebral haemorrhage in patients taking antithrombotic medicines. Caution should be exercised when considering the administration of antithrombotics because ARIA-H and ICHs greater than 1 cm in diameter have been observed in patients taking donanemab.

## CONCOMITANT ANTITHROMBOTIC TREATMENT

The majority of exposures to antithrombotic medicines were to acetylsalicylic acid (81%) and more than 20% were treated with anticoagulants. The use of concomitant aspirin and other antiplatelet therapy is permitted.

Based on the available evidence, it is not possible to make any definitive conclusions about the risk of ARIA-H/ICH with anticoagulants due to the small number of events and limited exposures in the clinical programme. If anticoagulation needs to be commenced during therapy with donanemab then donanemab should be paused. Donanemab therapy can be reinstated if anticoagulation is no longer medically indicated.

Additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with donanemab. Treatment with donanemab should not be initiated in patients receiving ongoing anticoagulant therapy.

As 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 in a patient being treated with donanemab. Advice from a radiologist should be immediately sought on appropriate MRI techniques for assessing patients with acute focal neurological deficits.

Use of thrombolytic agents should be avoided except for immediately life-threatening indications with no alternative management when the benefits could outweigh the risks.

# MONITORING AND MANAGING ARIA

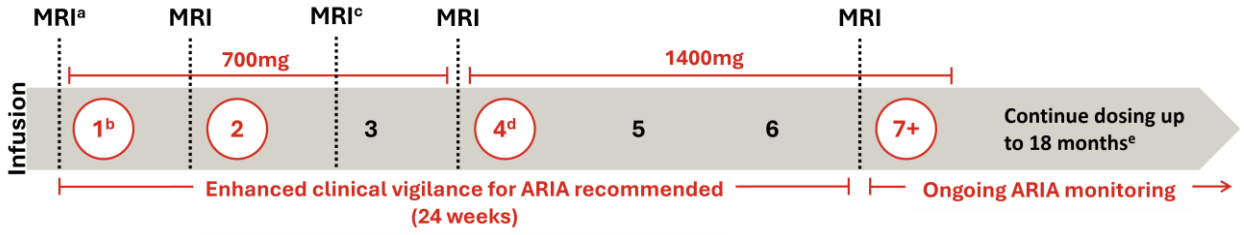
## PRIOR TO TREATMENT

Testing for APOE ε4 status should be performed prior to initiation of treatment. Prior to testing, patients should be appropriately counselled and consented according to national or local guidelines, as applicable. ARIA management and monitoring are not dependent on APOE ε4 status.

MRI scans are required prior to initiating treatment (within 1 year).

## DURING TREATMENT

**Perform and review an MRI prior to the second dose, prior to dose increase, and prior to the seventh dose, and if symptoms consistent with ARIA occur. Pre-dose MRIs must be reviewed before dosing.**




[a]Obtain and review a recent (within 1 year) brain MRI prior to initiating treatment with donanemab.
[b]Initial dose of 700mg.
[c]Additional MRI may be indicated in high-risk patients.
[d]Titrate up to 1400mg.
[e]Treatment should be maintained until amyloid plaques are cleared as confirmed using a validated method up to a maximum of 18 months. Treatment should be continued for up to 18 months if monitoring of amyloid plaque clearance with a validated method is not possible. If a patient progresses to moderate AD before the end of the 18 months maximum treatment, donanemab should be stopped.

- Patients should be reminded about the risk of ARIA at regular intervals during treatment
- If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated
- Donanemab should be permanently discontinued in patients who develop ICH >1 cm in diameter during treatment
- Suspend dosing for any symptomatic or radiographically moderate or severe ARIA-E and ARIA-H, until resolution (ARIA-E) or stabilisation (ARIA-H) of radiographic changes. A follow-up MRI to assess for resolution 2 to 4 months after initial identification should be performed. **Dose reduction is not recommended**
- Risk factors should be re-evaluated before re-starting treatment. Once the MRI demonstrates radiographic resolution (ARIA-E) or stabilisation (ARIA-H) and symptoms, if present, resolve, resumption of dosing should be guided by clinical judgment

## ARIA MRI CLASSIFICATION GRADING

| ARIA type | Radiographic severity | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| ARIA-E | Mild FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm | Moderate 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 | 5-9 new incident microhaemorrhages | ≥10 new incident microhaemorrhages |
| ARIA-H superficial siderosis[a] | 1 new focal area of superficial siderosis | 2 new focal areas of superficial siderosis | >2 new focal areas of superficial siderosis |

Abbreviations: FLAIR=fluid-attenuated inversion recovery.
[a]Includes new or increased focal areas of superficial siderosis.

## DIFFERENTIAL DIAGNOSIS

ARIA-E 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* GRE or SWI to detect ARIA-H and T2-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 (detected by MRI) may be mimicked by other pathologies such as ischaemic stroke and posterior reversible encephalopathy syndrome (PRES)
- ARIA can present with focal neurological findings that mimic ischaemic stroke. MRI should be used to evaluate stroke-like symptoms in patients on donanemab 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
- The risk of intracerebral haemorrhage with donanemab treatment is increased in patients receiving thrombolytic agent

## MANAGEMENT AND DOSING RECOMMENDATIONS FOR PATIENTS WITH ARIA

| | ARIA-E and ARIA-H severity on MRI | | |
|---|---|---|---|
| **Clinical symptom** | **Mild** | **Moderate** | **Severe**[a,b] |
| **Asymptomatic** | Consider suspending dosing | Suspend dosing | Suspend dosing |
| **Symptomatic** | Suspend dosing | | |

[a]If a second event of radiographically severe ARIA-H occurs, use clinical judgement in considering whether to restart or permanently discontinue treatment with donanemab.

[b]Evaluation of risk factors again prior to restarting is recommended. Supportive treatment, including corticosteroids may be considered in case of ARIA-E.