lormalzi®
(donanemab)

A Guide for Healthcare Professionals

Important Safety Information on Donanemab Treatment to Minimise Risk of Amyloid-Related Imaging Abnormalities (ARIA)

REPORTING OF ADVERSE EVENTS

Please report suspected adverse events (AEs) to HSA via their online reporting portal **(https://www.hsa.gov.sg/adverse-events)** and email a copy of the submitted HSA AE reporting form to **hec-pv.sin@dksh.com**.

Please provide as much information as possible when reporting. By reporting AEs, you can help provide more information on the safety of this medicine.

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) in patients with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD) receiving donanemab.

PATIENT ALERT CARD

Please provide the Patient Alert Card to your patients when they start treatment with donanemab. The card includes key information about the **patient's treatment,** the **signs and symptoms of ARIA/intracerebral haemorrhage (ICH)** and their **emergency contacts** to be shared with other healthcare professionals involved in their medical care.

Instruct your patients to immediately **report any new neurological symptoms**, to **always keep the Patient Alert Card with them** and to show it to any healthcare professional treating them.

To obtain copies of the Patient Alert Card, please contact a DKSH representative/Medical Science Liaison.

Electronic copies of this guide and the Patient Alert Card can be found on **https://www.hsa.gov.sg/educational-materials-for-HCP**.

Please scan the **QR code** to access the **full prescribing information for Lormalzi®**.

WHAT IS DONANEMAB?

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

INDICATION

Donanemab is indicated to slow disease progression in adult patients with AD. Treatment should be initiated in patients with evidence of Aß pathology and either MCI or mild dementia.

> The presence of Aß 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.

WHAT IS ARIA?

ARIA with oedema/effusions (ARIA-E) and ARIA with haemorrhage/haemosiderin deposition (ARIA-H) refer to a spectrum of magnetic resonance imaging (MRI) signal abnormalities associated with amyloid clearance in the brain. Monoclonal antibodies directed against Aß, including donanemab, can cause ARIA.

ARIA are usually asymptomatic, although serious and life-threatening events, including seizures and status epilepticus, can occur rarely. ARIA are detectable on brain MRI and 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 MRI prior to the third dose may aid in earlier detection of ARIA, particularly for patients with ARIA risk factors.

APOE ε4 carriers have a higher frequency (homozygotes greater than heterozygotes) of ARIA-E and ARIA-H compared to noncarriers. A higher frequency of ARIA has also been observed in patients with pre-treatment cerebral microhaemorrhage and/or superficial siderosis. Testing for APOE ε4 status and a recent brain MRI (within 1 year) must be performed prior to initiation of treatment to inform of the risk of developing ARIA.

Because ARIA-H and ICH greater than 1 cm in diameter have been observed in patients taking donanemab, exercise caution when considering the administration of anti-thrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to patients on donanemab. As ARIA can cause focal neurologic deficits that can mimic an ischaemic stroke, consider whether such symptoms could be due to ARIA before giving thrombolytic therapy to patients on donanemab.

SYMPTOMS OF ARIA

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

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.

Instruct your patients to seek **urgent medical attention** if they develop any features of ARIA.

ARIA-E

(vasogenic oedema and sulcal effusions)

ARIA-E was observed in 24.4% of patients treated with donanemab compared with 1.9% of patients on placebo.

- The maximum radiographic severity for ARIA-E was mild in 7.0% of patients, moderate in 14.8% of patients, and severe in 2.1% of patients.
- The majority of ARIA-E was asymptomatic with symptomatic ARIA-E reported for 5.8% 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 can occur spontaneously in patients with AD, independent of treatment. ARIA-H was observed in 31.3% of patients treated with donanemab compared with 13.0% of patients on placebo.

- The maximum radiographic severity for ARIA-H was mild in 14.8% of patients, moderate in 6.0% of patients, and severe in 10.4% of patients.
- The majority of ARIA-H was asymptomatic, with symptomatic ARIA-H reported for 1.0% of patients treated with donanemab compared with 0.3% of patients on placebo.
- Isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) was observed in 12.5% of donanemab treated patients compared to 11.7% on placebo.

INTRACEREBRAL HAEMORRHAGE >1 CM

ICH >1 cm in diameter was reported in 0.3% of patients treated with donanemab compared to 0.2% of patients on placebo.

Monitor your patients for indicators of ICH throughout donanemab treatment.

MONITORING AND MANAGING ARIA

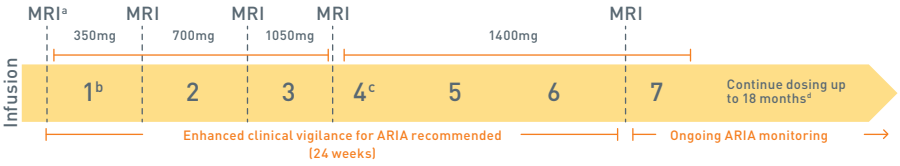
PRIOR TO TREATMENT

Testing for APOE ε4 status and a recent brain MRI (within 1 year) must be performed prior to initiation of treatment. ARIA management and monitoring are not dependent on APOE ε4 status.

The safety of donanemab has not been established in patients with pre-treatment MRI showing ARIA-E, more than 4 microhaemorrhages, more than 1 area of superficial siderosis, severe white matter disease or intracerebral haemorrhage greater than 1 cm. Exercise caution when initiating donanemab treatment in patients with these baseline risk factors.

DURING TREATMENT

Perform and review a brain MRI prior to the second, third, fourth and seventh doses, 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 350mg.*

[c] *Titrate up to 1400mg.*

[d] *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.*

- Remind patients about the risk of ARIA at regular intervals during treatment.
- Perform clinical evaluation, including MRI if indicated, if a patient experiences symptoms suggestive of ARIA.
- 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 and symptoms, if present, resolve. A follow-up MRI to assess for resolution 2 to 4 months after initial identification should be performed.
- Risk factors should be re-evaluated before re-starting treatment. Resumption of dosing should be guided by clinical judgement.

ARIA MRI CLASSIFICATION GRADING

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	5-9 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;

ARIA-E = amyloid-related imaging abnormalities-oedema/effusions; ARIA-H = amyloid-related imaging abnormalities haemorrhage/haemosiderin deposition

[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 donanemab 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 recalled echo (GRE) or susceptibility-weighted imaging (SWI) to detect ARIA-H and T2- 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.

MANAGEMENT AND DOSING RECOMMENDATIONS FOR PATIENTS WITH ARIA

Clinical Symptom	ARIA-E and ARIA-H severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	Consider suspending dosing	Suspend dosing[a]	Suspend dosing[a]
Symptomatic	Suspend dosing[a]		

[a]*Suspend until MRI demonstrates radiographic resolution (ARIA-E) or stabilisation (ARIA-H) and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution (ARIA-E) or stabilisation (ARIA-H) 2 to 4 months after initial identification. Resumption of dosing or discontinuation should be guided by clinical judgement. Evaluation of risk factors again prior to restarting is recommended. Supportive treatment, including corticosteroids, may be considered in case of ARIA-E.*

This document has been approved by HSA as of 11/03/2025.

DKSH Singapore Pte Ltd
47 Jalan Buroh, #09-01, Singapore 619491
Phone +65 6471 1466