Kisunla®

(donanemab)

17.5 mg/mL

Concentrate for solution for infusion

Summary of Risk Management Plan (RMP)

Eli Lilly (Suisse) SA

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Summary of Risk Management Plan for Kisunla (Donanemab)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP Summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Kisunla is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Kisunla in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Eli Lilly (Suisse SA) is fully responsible for the accuracy and correctness of the content of the published summary RMP of Kisunla.

I - The Medicine and What It is Used for

Kisunla is authorised for the treatment of adults with early symptomatic AD who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers (see SmPC for the full indication). It contains donanemab as the active substance and it is given by IV infusion.

Further information about the evaluation of Kisunla's benefits can be found in Kisunla's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Kisunla, together with measures to minimise such risks and the proposed studies for learning more about Kisunla's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Kisunla, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Kisunla is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Kisunla are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kisunla. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	ARIA-E (cerebral oedema/effusion) ARIA-H (cerebral microhaemorrhage and superficial siderosis) Hypersensitivity events (including IRR)
Important potential risks	Intracranial haemorrhage
Missing information	None

Abbreviations**:** ARIA-E (cerebral oedema/effusions) = amyloid-related imaging abnormalities–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = amyloid-related imaging abnormalities–haemorrhage/hemosiderin deposition; IRR = infusion-related reaction.

II.B Summary of Important Risks

Important Identified Risk: ARIA-E (cerebral oedema/effusion)	
Evidence for linking the risk to the medicine	ARIA-E is a known class effect of amyloid-targeting therapies. Patients with ARIA-E are usually asymptomatic. If symptoms occur, these may include, but are not limited to, headache, vomiting, unsteadiness, dizziness, tremor, confusion, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures (Ostrowitzki et al. 2012; Sperling et al. 2012; VandeVrede et al. 2020; Mintun et al. 2021; Swanson et al. 2021). Intervention beyond withholding treatment may be required to address concomitant symptoms (e.g., corticosteroids). Events of ARIA-E were observed across the donanemab clinical development programme.
Risk factors and risk groups	In the donanemab clinical development programme, a higher frequency of ARIA-E was observed in participants with baseline risk factors that included ApoE ε4 carriers and pre-treatment baseline MRI microhaemorrhages and/or superficial siderosis. In the Dona-PC, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 41.7%, heterozygote 24.1%) compared to non-carriers (14.8%). Additionally, the frequency of symptomatic ARIA-E in ApoE ε4 carriers (homozygote 7.7%, heterozygote 6.1%) was increased compared to non-carriers (4.1%). In the Study AACI-PC, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 41.3%, heterozygote 23.2%) compared to non-carriers (15.7%). Additionally, the frequency of symptomatic ARIA-E in ApoE ε4 carriers (homozygote 8.4%, heterozygote 6.6%) was increased compared to non-carriers (3.9%). In the All-Dona, the frequency of ARIA-E was higher in donanemab-treated ApoE ε4 carriers (homozygote 33.9%, heterozygote 20.2%) compared with non-carriers (11.6%). A higher frequency of symptomatic ARIA-E was also noted for donanemab-treated patients ApoE ε4 carriers (homozygote 6.6%, heterozygote 4.3%) compared with non-carriers (3.2%).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.8; legal status and Sections 2 and 4 of the PIL **Additional risk minimisation measures:** • HCP educational material, including prescriber checklist • Patient card • Controlled access programme including regular report of observations reported to Swissmedic via the PSUR/PBRER. The proposed CAP has 2 important mechanisms to mitigate risk: o restricting access of donanemab to centres corresponding to the Swissmedic defined criteria, and

	○ implementing a registration system to assist HCPs in ▪ assessing patient eligibility ▪ providing quick reference to educational materials, and ▪ confirming adherence to the materials.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. ○ Follow-up time in the registry will be extended in the EU registry-based observational study from 12 months post donanemab initiation to 2 years (24 months). Donanemab- treated patients will be followed "as-treated" to the earliest of drug discontinuation + a risk extension, 24 months post-donanemab initiation, patient death and/or registry exit) for safety analyses and to the earliest of 24 months, patient death and/or registry exit for cognitive/functional endpoints. ○ A subgroup analysis to evaluate the protocol-defined safety events among patients in the registry who do not clear amyloid by 18 months will be added. ○ A final study report from the EU study will be provided to Swissmedic once completed. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU. • Secondary database study to characterise safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU (study identifier pending) ○ An addendum to the study protocol will be executed to add a Swiss database (e.g. insurance database or another claims/electronic health records database) to the study. ○ A final study report, including results from the EU databases and the Swiss database, will be provided once completed. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: ARIA-H (cerebral microhaemorrhage and superficial siderosis)	
Evidence for linking the risk to the medicine	ARIA-H is a known class effect of amyloid-targeting therapies (Arrighi et al. 2016). Patients with ARIA-H are usually asymptomatic. ARIA-H may be related to vascular amyloid clearance with weakening and rupture of small blood vessels (Withington 2022). Whereas ARIA-E is usually radiographically visible over the course of weeks or months, ARIA-H can remain permanently visible on subsequent imaging (Salloway 2022). If symptoms occur, they may include headache, worsening confusion,

	dizziness, visual disturbances, nausea, and seizures (Withington 2022). Cases of ARIA-H were observed across the donanemab clinical development programme.
Risk factors and risk groups	In the clinical development programme of donanemab, a higher frequency of ARIA-H was observed in participants with baseline risk factors that included ApoE ε4 carriers and pre-treatment baseline MRI microhaemorrhages and/or superficial siderosis. In addition, risk factors that have been associated with ARIA-H also include the use of antithrombotic medication (Arrighi et al. 2016). In the Dona-PC, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 53.6%, heterozygote 31.0%) compared with non-carriers (18.9%). Additionally, the frequency of symptomatic ARIA-H in donanemab-treated participants ApoE ε4 carriers (homozygote 1.2%, heterozygote 1.3%) was increased compared with non-carriers (0.3%). In the AACI-PC, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 50.3%, heterozygote 32.5%) compared with non-carriers (18.8%). Additionally, the frequency of symptomatic ARIA-H in donanemab-treated participants ApoE ε4 carriers (homozygote 1.4%, heterozygote 1.5%) was increased compared with non-carriers (0.4%). In All-Dona, the frequency of ARIA-H was higher in donanemab-treated ApoE ε4 carriers (homozygote 43.2%, heterozygote 26.2%) compared to non-carriers (16.6%). The frequency of symptomatic ARIA-E was slightly higher in donanemab-treated participants ApoE ε4 carriers (homozygote 0.7%, heterozygote 0.6%) compared with non-carriers (0.3%).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8; legal status and Sections 2 and 4 of the PIL **Additional risk minimisation measures:** • HCP educational material including prescriber checklist • Patient card • Controlled access programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Hypersensitivity events (including IRR)	
Evidence for linking the risk to the medicine	Biological drugs represent foreign protein and thereby can elicit immediate and non-immediate hypersensitivity events, including IRRs and anaphylaxis (Maggi et al. 2011).

	Immediate hypersensitivity reactions, including IRRs are associated with donanemab treatment and have been observed across the donanemab clinical development programme.
Risk factors and risk groups	No specific risk factors have been identified for hypersensitivity reactions. In clinical studies, 88.1% of donanemab-treated patients developed ADAs and all of the patients with ADA had neutralising antibodies. All patients reporting IRRs had ADA. Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.3, 4.4, 4.8; legal status and Sections 2 and 4 of the PIL **Additional risk minimisation measures:** • Controlled access programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Intracranial haemorrhage	
Evidence for linking the risk to the medicine	Serious (including fatal) cases of intracranial haemorrhage have been observed with amyloid-targeting therapies including donanemab. In the donanemab clinical development programme, intracranial haemorrhage was observed at a higher frequency in donanemab-treated patients (1.3% in both Dona-PC and AACI-PC) than placebo (0.8% in both Dona-PC and AACI-PC). The largest difference between groups was observed for events of subdural haematoma, which were higher in the donanemab group (0.5% in both Dona-PC and AACI-PC) than placebo (0.2% in both Dona-PC and AACI-PC). Most of the subdural haematoma or subdural haemorrhage events were temporally associated with head trauma or fall. Events of intracerebral haemorrhage greater than 1cm (also referred to as macro-haemorrhage) including haemorrhagic stroke and cerebral haemorrhage were observed at a similar frequency in participants treated with either donanemab (0.3% in Dona-PC and 0.4% in AACI-PC) or placebo (0.2% in both Dona-PC and AACI-PC). In All Dona, intracranial haemorrhage was observed in 1.3% of the participants, driven by subdural haematoma (0.4%) and subarachnoid haemorrhage (0.3%). Cerebral haemorrhage (0.1%) and haemorrhagic stroke (0.1%) were less frequent. In All-Dona, 3 fatal intracranial haemorrhages were reported in donanemab-treated participants. These 3 participants with fatal outcomes were at increased risk of intracranial haemorrhage due to history of

	hypertension, stroke, thrombolytic use, or the event being temporally associated with head trauma or fall. To date, there has been no clear evidence of an increased risk of intracranial haemorrhage in patients exposed to donanemab during clinical development. Therefore, intracranial haemorrhage is considered an important potential risk for donanemab and will be further characterised in ongoing clinical trials and planned post-marketing observational studies.
Risk factors and risk groups	Overall, concomitant antithrombotic use did not impact the frequency, severity or seriousness of intracranial haemorrhagic events. The most frequently used antithrombotic was aspirin (approximately 80%), followed by anticoagulants (greater than 20%). Analysis of antithrombotic medication type, (aspirin, non-aspirin antiplatelets, and anticoagulants) did not reveal any patterns different than that observed for antithrombotics overall. Given the limited number of exposures to thrombolytics, no conclusions can be made regarding the risk of intracranial haemorrhage with concomitant thrombolytic use. Risk factors specifically associated with intracerebral haemorrhage in patients with AD include ApoE ε4 alleles, pre-existing cerebral microhaemorrhages, and CAA (Arrighi et al. 2016; Cummings et al. 2023). Given the small number of haemorrhagic events in the donanemab placebo-controlled studies, an association of intracranial haemorrhagic events with ApoE ε4 carrier state could not be established. All the above-mentioned risk factors might further increase the risk for haemorrhagic complications during thrombolytic or antithrombotic therapies (Reisz et al. 2022; Cummings et al. 2023).
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8; legal status and Section 2 of the PIL **Additional risk minimisation measures:** • HCP education material, including prescriber checklist • Patient Card • Controlled access programme
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational studies: • Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU. • Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU. • Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU. See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: ADA = antidrug antibody; AD = Alzheimer's disease; ApoE ε4 = apolipoprotein subtype E allele 4; ARIA = amyloid-related imaging abnormality; ARIA-E (cerebral oedema/effusions) = ARIA–oedema/effusions; ARIA-H (cerebral microhaemorrhage and superficial siderosis) = ARIA–haemorrhage/hemosiderin deposition; CAA = cerebral amyloid angiopathy; EU = European Union; IRR = infusion-related reaction; MRI = magnetic resonance imaging; PIL = patient information leaflet; SmPC = summary of product characteristics.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

Following studies are a condition of the marketing authorisation or specific obligation of Kisunla.

Study short name and title: Secondary database study to characterise the safety, drug utilisation, and effectiveness of additional risk minimisation activities in donanemab-treated patients in the EU.

Rationale and study objectives: This study includes 3 categories of objectives:

- Objective 1: Safety events
- Objective 2: Drug utilisation
- Objective 3: Effectiveness of additional risk minimisation activities

Serious hypersensitivity and intracranial haemorrhage events have been observed in the donanemab clinical development programme. This large secondary database study will provide the opportunity to describe the incidence of these infrequent events in EU patients treated with donanemab as part of real-world practice, including real-world subgroups that may have been underrepresented or excluded from the clinical development programme. Understanding donanemab drug utilisation in the real-world EU patient populations results in the following:

1. Accumulation of information regarding the use of donanemab in populations not studied in clinical trials (for example, patients with Down syndrome), use of donanemab by patients with risk factors for safety outcomes and whether the use is consistent with the donanemab label.
2. Insight into effectiveness of additional risk minimisation activities: the HCP educational materials.

The objectives of this study are as follows:

- Objective 1 (safety events): To describe the incidence of serious hypersensitivity events (as defined by hospitalisation, for example, due to anaphylaxis) and intracranial haemorrhage in patients with AD treated with donanemab. The incidence of intracranial haemorrhage will additionally be described within the subgroup of patients using concomitant antithrombotic or thrombolytic medications.
- Objective 2 (drug utilisation): To describe donanemab drug utilisation in terms of dose, length of treatment, and user demographics/characteristics overall and within the following subgroups: Patients with Down syndrome, and patients using concomitant antithrombotic or thrombolytic medications.

- Objective 3 (effectiveness of additional risk minimisation activities): To monitor the compliance to recommendations before donanemab treatment initiation and during donanemab treatment.

Study short name and title: Registry-based observational study to characterise ARIA within a cohort of donanemab-treated patients in the EU.

Rationale and study objectives: ARIA-E and ARIA-H were observed in clinical trials and are important identified risks for donanemab in the EU RMP.

The primary objective of this study is to describe the incidence and severity of symptomatic ARIA (ARIA-E and ARIA-H) within a cohort of donanemab-treated patients in real-world clinical practice in the EU. Symptomatic ARIA will be assessed in patients that receive donanemab based on MRI scans performed as part of routine care and the presence of ARIA-related symptoms. An additional primary objective is to characterise long-term cognitive outcomes and disease progression of patients with ARIA to assess whether these events are associated with accelerated cognitive decline or changes in the rate of disease progression. Secondary outcomes will include asymptomatic ARIA, hypersensitivity events, and intracranial haemorrhage. Intracranial haemorrhage will be described within the subgroup of patients receiving concomitant antithrombotic or thrombolytic medications. Patients with ARIA (symptomatic or asymptomatic) will be followed to document real-world interventions and radiographic resolution or stabilisation over time. All ARIA events will be described within the overall study population and within subgroups of ApoE ε4 genotype (heterozygote or non-carrier). Additional patient characterisation will include description of baseline demographics, comorbidities, and co-medications (including the use of antithrombotic and thrombolytic medications).

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name and title: Healthcare provider survey to assess the effectiveness of the donanemab additional risk minimisation activities in the EU.

Rationale and study objectives: Additional risk minimisation activities will be implemented for donanemab. These activities include the following:

- To promote the safe and effective use of donanemab, initiation of treatment in all patients should be captured in the “EU CAP Registration System” implemented as part of the CAP. Use of donanemab treatment 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.
- Educational material for prescribers and radiologists on important safety risks related to the use of donanemab that is ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage. It will also inform HCPs about the indicated patient population, contraindications, information about the donanemab CAP, and the importance of the patient card, including carrying it at all times and to provide to HCPs in emergency situations. In addition, a prescriber checklist that includes guidance on initial and subsequent treatment, and recommendations for assessments before and during treatment with donanemab.

- A patient card designed to enhance the awareness and knowledge of patients and caregivers about the safety concerns with donanemab as well as inform physicians of ARIA differential diagnosis in an emergency setting.

The objectives of the survey are to assess the following:

1. Prescriber and radiologist understanding of the important safety risks related to the use of donanemab detailed in the HCP educational materials, that is, information relating to ARIA-E (cerebral oedema/effusion), ARIA-H (cerebral microhaemorrhage and superficial siderosis), and intracranial haemorrhage.
2. Prescriber and radiologist self-reported adherence to the risk minimisation practices.
3. Prescriber knowledge of the prescriber checklist, including guidance on initial and subsequent treatment and recommendation for assessments, before and during treatment with donanemab.
4. Prescriber distribution of the patient card to patients prescribed donanemab for the first time.
5. Prescriber awareness and use of the CAP.