1. NAME OF THE MEDICINAL PRODUCT

Kisunla

Patient safety information card
The marketing of Kisunla is subject to a risk management plan (RMP), including a "Patient safety information card". The "Patient safety information card" emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

Prescriber guide
This product is marketed with a prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 350 mg donanemab in 20 mL (17.5 mg/mL).

Donanemab is a recombinant monoclonal humanised antibody produced in Chinese Hamster Ovary (CHO) cells.

Excipient(s) with known effect

Each 20 mL vial contains 11.5 mg sodium and 4 mg polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The solution is clear to opalescent, colourless to slightly yellow to slightly brown with a pH of 5.5 – 6.5 and an osmolarity of approximately 300 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kisunla is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology (see section 4.4).

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the diagnosis and treatment of Alzheimer's disease (AD) with timely access to Magnetic Resonance Imaging (MRI). Donanemab should be administered under the supervision of a multidisciplinary team trained in detection, monitoring and management of amyloid-related imaging abnormalities (ARIA) and experienced in detecting and managing infusion related reactions (IRR).

Patients treated with donanemab must be given the patient card and be informed about the risks of donanemab (see also package leaflet).

ApoE ε4 Testing

ApoE ε4 genotype should be assessed by a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see section 5.1).

Testing for ApoE ε4 status should be performed prior to initiation of treatment with donanemab to inform the risk of developing ARIA (see sections 4.1 and 4.4). Prior to testing patients should be appropriately counselled and consented according to national or local guidelines, as applicable.

Posology

Beta amyloid evidence consistent with AD should be confirmed using a validated test (e.g. positron emission tomography [PET] scan, cerebrospinal fluid [CSF] or another appropriate test).

Donanemab should be administered every 4 weeks. The recommended dose of donanemab is 350 mg for the first dose, 700 mg for the second dose, 1,050 mg for the third dose, followed by 1,400 mg every 4 weeks. Treatment should be maintained until amyloid plaques are cleared (e.g. at 6 or 12 months, see section 5.1) as confirmed using a validated method. The maximum treatment duration is 18 months which should not be exceeded even if plaque clearance is not confirmed.

The benefit-risk of treatment should be reassessed at regular intervals on an individual basis and considering the rate of disease progression.

Consideration should be given to discontinuing treatment before the end of the 18 months maximum treatment if patients progress to moderate AD.

Missed dose

If an infusion is missed, administration should be resumed every 4 weeks at the same dose as soon as possible.

Monitoring, dosing interruption, and treatment discontinuation for amyloid related imaging abnormalities

Donanemab can cause ARIA, characterized as ARIA with oedema (ARIA-E), which can be observed on MRI as brain oedema or sulcal effusions, and ARIA with haemosiderin deposition (ARIA-H), which includes microhaemorrhage and superficial siderosis. In addition to ARIA, intracerebral haemorrhages greater than 1 cm in diameter have occurred in patients treated with donanemab.

A recent (within 6 months) brain MRI should be available prior to initiating treatment with donanemab to evaluate for pre-existing ARIA. An MRI should be performed prior to the second dose (at 1 month), prior to the third dose (at 2 months), prior to the fourth dose (at 3 months), and prior to the seventh dose (at 6 months). An additional MRI at one year of treatment (prior to the twelfth dose) in patients with ARIA risk factors such as ApoE ε4 heterozygotes, and/or patients with previous ARIA events earlier in treatment, should be performed. If a patient experiences symptoms suggestive of ARIA at any time during treatment, clinical evaluation should be performed including an MRI (see section 4.4).

The recommendations for dosing interruptions or treatment discontinuation for patients with ARIA-E and ARIA-H are provided in Table 1.

Table 1: Dosing recommendations for patients with ARIA-E and ARIA-H

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

[a]See Table 2 for ARIA MRI radiographic severity classification criteria

In case of asymptomatic mild ARIA, consider dose suspension based on radiological features of ARIA, number of ARIA episodes and clinical condition.

In case of asymptomatic moderate ARIA and symptomatic mild/moderate ARIA, suspend dose until MRI demonstrates radiographic resolution (ARIA-E) or stabilisation (ARIA-H) and symptoms, if present, resolve. A follow-up MRI to assess for resolution (ARIA-E) or stabilization (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 stabilization should be guided by clinical judgment including re-evaluation of risk factors (see section 4.4). Standard supportive treatment, including corticosteroids may be considered in case of ARIA-E (see section 4.8).

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.

Clinical judgment should be used 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.

Special populations

Renal impairment/hepatic impairment
No dose adjustment is required in patients with renal impairment or hepatic impairment (see section 5.2).

Paediatric population
There is no relevant use of donanemab in the paediatric population for the treatment of Alzheimer's disease.

Method of administration

Donanemab is for intravenous use only. Each vial is for single use only. Diluted solution should be administered over a period of at least 30 minutes. Patients should be observed post-infusion for a minimum of 30 minutes. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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).
- Patients with bleeding disorders that are not under adequate control.
- Initiation in patients receiving ongoing anticoagulant therapy (see section 4.4).

- Severe white matter disease (see section 4.4).
- Patients with poorly controlled hypertension.
- Conditions that do not allow MRI assessment, including claustrophobia or the presence of metal (ferromagnetic) implants/cardiac pacemaker.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Amyloid beta pathology

The presence of amyloid beta pathology must be confirmed via an appropriate test prior to initiating treatment.

Amyloid-related imaging abnormalities (ARIA)

ARIA-H generally occurs in association with an occurrence of ARIA-E.

ARIA has been observed very commonly in donanemab clinical studies. ARIA usually occurs early in treatment and is usually asymptomatic. When present, reported symptoms associated with ARIA may include headache, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures. Symptoms associated with ARIA usually resolve over time (see section 4.8). Following an initial event of ARIA, the rate of recurrence on resumption of treatment with donanemab is very common; 24.3 % in those with ARIA-E and 35.9 % in those with ARIA-H (see section 4.8). Serious cases of ARIA have been observed and some have been fatal (see section 4.8). ARIA can be detected by MRI and while ARIA-E typically resolves on imaging, ARIA-H may persist and stabilise.

Most ARIA events were first observed within 24 weeks of initiation of treatment. Most serious ARIA events occurred within 12 weeks of initiation of treatment. Access to MRI should be available during the treatment period of donanemab. Given preexisting risk factors, patients who are eligible for amyloid treatment therapies are also at risk for spontaneous ARIA. ARIA should be considered as a possible aetiology for neurological symptoms.

The benefit of donanemab for the treatment of AD and potential risk of serious adverse reactions associated with ARIA should be considered when deciding to initiate treatment with donanemab (see section 4.8).

MRI monitoring for ARIA
Baseline brain MRI and periodic monitoring with MRI are recommended (see section 4.2). Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with donanemab.

If a patient experiences symptoms suggestive of ARIA (see section 4.8), clinical evaluation should be performed, including additional MRI testing (see sections 4.2 and 4.4 “Amyloid-related imaging abnormalities - ARIA”).

Recommendations for dosing interruptions and treatment discontinuations in patients with ARIA
If symptoms of ARIA-H occur, it is often in the presence of ARIA-E and managed as for ARIA-E. The recommendations for dosing interruptions and treatment discontinuations for patients with ARIA-E and ARIA-H are provided in Table 1 (see section 4.2).

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

Radiographic severity
The radiographic severity of ARIA associated with donanemab was classified by the criteria shown in Table 2.

Table 2: ARIA MRI Classification criteria

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

ApoE ε4 carrier status and risk of ARIA
ApoE ε4 carriers have a higher frequency (homozygotes greater than heterozygotes) of ARIA-E and ARIA-H, including serious and symptomatic ARIA, compared to non-carriers. Donanemab is not indicated in patients who are ApoE ε4 homozygotes (see section 4.1). Testing for ApoE ε4 carrier status should be performed prior to initiation of treatment to inform the risk of developing ARIA (see section 4.2). Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes.

Increased intracerebral haemorrhage risk
Caution should be exercised when considering the use of donanemab in patients with factors that indicate an increased risk for intracerebral haemorrhage.
Intracerebral haemorrhages greater than 1 cm in diameter including fatal events have occurred in patients treated with donanemab (see section 4.8).

Concomitant antithrombotic treatment

Baseline use of antithrombotic medicinal products (aspirin, other antiplatelets, or anticoagulants) was allowed in clinical trials with donanemab. The majority of exposures to antithrombotic medicines were to acetylsalicylic acid.

Patients who received donanemab and an antithrombotic medicine (acetylsalicylic acid, other antiplatelets, or anticoagulants), did not present with an increased frequency of ARIA. The number of events and the limited exposure to non-acetylsalicylic acid antithrombotic medicines limit definitive conclusions about the risk of ARIA or intracerebral haemorrhage in patients taking antithrombotic medicines.

Because intracerebral haemorrhages greater than 1 cm in diameter have been observed in patients taking donanemab and in patients receiving antithrombotic agents during donanemab treatment, 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:

- 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 (e.g., pulmonary embolism with haemodynamic compromise) when the benefits could outweigh the risks. The benefits and risks of treatment should be individually reconsidered by the specialist physician and the patient.

ARIA can cause focal neurologic deficits similar to those observed in an ischaemic stroke. Clinicians treating ischemic 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 ischemic stroke rather than ARIA is the etiology, and inform use of thrombolytics or thrombectomy when appropriate.

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

Other risk factors for ARIA and intracerebral haemorrhage
In the donanemab clinical trials, 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 (see section 4.3). A higher frequency of ARIA has been observed in patients with pre-treatment cerebral microhaemorrhage and/or superficial siderosis. Donanemab treatment is contra-indicated in patients with baseline superficial siderosis and patients with > 4 microhaemorrhages at baseline (see section 4.3).
The presence of an ApoE ε4 allele is associated with CAA, which has an increased risk for intracerebral haemorrhage.

Individual benefit-risk based on tau pathology

The benefit-risk may depend on the level of baseline tau. Numerically higher levels of efficacy have been observed in patients with low-medium tau compared to high tau (see section 5.1). The clinical efficacy in patients with no or very low levels of tau has not been established. The results of tau pathology testing, if performed, should be considered in individual patient benefit-risk discussions.

Infusion-related reactions

Infusion-related reactions have been observed commonly with administration of donanemab (see section 4.8). These reactions may uncommonly be severe or life-threatening and/or include anaphylaxis, and typically occur during infusion or within 30 minutes post infusion. Signs and symptoms of infusion-related reactions may include erythema, chills, nausea, vomiting, sweating, headache, chest tightness, dyspnoea, and changes in blood pressure.

Administration of donanemab should be discontinued immediately and appropriate treatment should be initiated in case of serious infusion-related reactions or as clinically indicated.

Immunogenicity

In placebo controlled clinical studies, 88.1 % of donanemab-treated patients developed anti-drug antibodies (ADA) and all of the patients with ADA had neutralising antibodies. All patients reporting

infusion-related reactions had ADA. Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.

Patients excluded from clinical trials (see also section 5.1)

Patients with Down syndrome may be associated with a higher rate of CAA and ARIA events. Patients with Down syndrome have not been studied in clinical trials with donanemab. The safety and efficacy of donanemab in these patients is unknown.

Sodium

This medicinal product contains 46 mg sodium per 1,400 mg dose, equivalent to 2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

When prepared with sodium chloride 9 mg/mL (0.9 %) solution for injection, the amount of sodium contributed by the sodium chloride diluent will range from 53 mg (for 350 mg dose diluted to 10 mg/mL) to 956 mg (for 1,400 mg dose diluted to 4 mg/mL), equivalent to 3 % - 48 % of the WHO recommended maximum daily intake. This is in addition to the amount contributed by the medicinal product.

Polysorbate 80

This medicinal product contains 16 mg of polysorbate 80 in each 1,400 mg dose of medicinal product which is equivalent to approximately 0.23 mg/kg. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No pharmacokinetic drug interactions are expected based on the characteristics of donanemab.

ARIA-H and intracerebral haemorrhages greater than 1 cm in diameter have been observed in patients taking donanemab. Therefore, caution should be exercised when considering the administration of antithrombotics since the risk for intracerebral haemorrhages with donanemab may be increased (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of donanemab in pregnant women. A weight-of-evidence approach does not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of donanemab during pregnancy.

Breast-feeding

It is unknown whether donanemab is excreted in human milk. Human immunoglobulin G (IgG) is known to be excreted in breast milk during the first days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to breast-fed infants cannot be excluded during this short period. Afterwards, use of donanemab could be considered during breast-feeding only if clinically needed.

Fertility

There are no data on the effects of donanemab on human fertility. No animal studies have been performed to test donanemab for potential fertility impairment.

4.7 Effects on ability to drive and use machines

Donanemab has major influence on the ability to drive and use machines if neurological deficits occur, for example visual disturbances, alteration of consciousness and seizures (section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In a placebo-controlled pivotal study including patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease (see section 5.1), a total of 853 adult subjects received at least one dose of donanemab. Of these, 710 participants concerned the indicated population (ApoE ε4 heterozygotes and non-carriers).

Based on the ApoE ε4 carrier status of the patients treated with donanemab, 29.9 % (255/853) were non-carriers, 53.0 % (452/853) were heterozygotes and 16.8 % (143/853) were homozygotes. With the exception of events of ARIA, the safety profile was similar across genotypes.

The most frequently reported adverse reactions were ARIA-E (20.6 %), ARIA-H (27.6 %), and headache (14.6 %). The most important serious adverse reactions were: Serious ARIA-E (1.3 %), serious ARIA-H (0.3 %), and serious hypersensitivity, including infusion-related reactions (0.4 %). Anaphylactic reaction was uncommonly reported (0.4 %) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions from clinical studies with donanemab (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 3. Adverse reactions

System organ class	Very common	Common	Uncommon
Nervous system disorders	ARIA-E[a,b] ARIA-H[a,b] Microhaemorrhage Superficial siderosis Headache	Intracranial haemorrhage[c]	
Gastrointestinal disorders		Nausea Vomiting	
Injury, poisoning and procedural complications		Infusion-related reaction[d] Hypersensitivity	Anaphylactic reaction

[a] As assessed by MRI.
[b] Symptoms may include headache, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures.
[c] Includes subdural haematoma, subarachnoid haemorrhage, cerebral haemorrhage, haemorrhagic stroke and cerebrovascular accident.
[d] Signs and symptoms of infusion-related reactions and hypersensitivity may include erythema, chills, nausea, vomiting, sweating, headache, chest tightness, dyspnoea, and changes in blood pressure.

Description of selected adverse reactions

Amyloid-related imaging abnormalities in the indicated population

In the pivotal placebo-controlled study, where donanemab was administered at the dosing regimen of 700 mg every 4 weeks for the first 3 doses, and then 1,400 mg every 4 weeks, ARIA (ARIA-E or ARIA-H) was observed in 33 % (234/710) of ApoE ε4 heterozygotes and non-carrier patients treated with donanemab, compared to 13.5 % (98/728) of heterozygotes and non-carrier patients on placebo. Serious ARIA events were reported for 1.4 % (10/710) of patients treated with donanemab. Fatal cases of ARIA due to donanemab occurred uncommonly in the pivotal study (0.4 %, three patients). Clinical symptoms associated with ARIA-E resolved in approximately 80 % of patients. ARIA-E symptoms may include headache, confusion, nausea, vomiting, unsteadiness, dizziness, tremor, visual disturbances, speech disturbances, worsening cognitive function, alteration of consciousness, and seizures.

ARIA-E was observed in 20.6 % (146/710) of ApoE ε4 heterozygotes and non-carrier patients treated with donanemab compared with 1.8 % (13/728) of patients on placebo. The maximum radiographic severity for ARIA-E was mild in 6.2 % (44/710) of patients, moderate in 12.7 % (90/710) of patients, and severe in 1.4 % (10/710) of patients. Symptomatic ARIA-E was reported for 5.6 % (40/710) of patients treated with donanemab in the pivotal study. The median time to resolution of ARIA-E was approximately 8.3 weeks. Of the donanemab-treated patients with ARIA-E, approximately 24.3 % (35/144) experienced multiple episodes of ARIA-E.

ARIA-H was observed in 27.6 % (196/710) of ApoE ε4 heterozygotes and non-carrier patients treated with donanemab compared with 12.2 % (89/728) of patients on placebo. The maximum radiographic severity for ARIA-H was mild in 14.4 % (102/710) of patients, moderate in 5.5 % (39/710) of patients, and severe in 7.6 % (54/710) of patients. Symptomatic ARIA-H was reported for 1.1 % (8/710) of patients treated with donanemab compared with 0.3 % (2/728) of patients on placebo. Isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) was observed in 12.4 % (88/710) of donanemab-treated patients compared to 11.5 % (84/728) on placebo. Of the donanemab-treated patients with ARIA-H, approximately 35.9 % (70/195) of participants experienced multiple episodes of ARIA-H.

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.

Standard supportive treatment, including corticosteroids may be considered in case of ARIA-E, however the effectiveness of treatment has not been established.

Intracranial haemorrhage in the indicated population
Intracranial haemorrhage was reported in 1.4 % (10/710) of ApoE ε4 heterozygotes and non-carrier patients after treatment with donanemab compared to 0.8 % (6/728) of patients on placebo. Of these, intracerebral haemorrhage greater than 1 cm was observed in 0.4% (3/710) of donanemab-treated patients and in 0.3 % (2/728) in placebo treated patients. Additionally, in a participant with baseline superficial siderosis treated with donanemab in the pivotal study, fatal ARIA-H was reported with concurrent intracerebral haemorrhage.

ApoE ε4 carrier status and risk of ARIA
In the pivotal study, the overall incidence of ARIA was lower in non-carriers (24.7 % donanemab vs. 12.0 % placebo) and heterozygotes (37.6 % donanemab vs. 14.1 % placebo) than in homozygotes (55.9 % donanemab vs. 21.9 % placebo). Among patients on donanemab, ARIA-E occurred in 15.7 % of non-carriers and 23.2 % of heterozygotes compared to 41.3 % of homozygotes. Symptomatic ARIA-E occurred in 3.9 % of non-carriers and 6.6 % of heterozygotes compared to 8.4 % of homozygotes. ARIA-H occurred in 18.8 % of non-carriers and 32.5 % of heterozygotes compared to 50.3 % of homozygotes. Symptomatic ARIA-H occurred in 0.4 % of non-carriers, in 1.5 % of

heterozygotes and in 1.4 % of homozygotes. Serious ARIA occurred in 0.8 % of non-carriers and 1.8 % of heterozygotes compared to 2.8 % of homozygotes.

Infusion-related reactions in the indicated population
In the pivotal placebo-controlled study, infusion reactions were observed in 8.3 % of patients treated with donanemab compared to 0.4 % on placebo. Anaphylactic reaction was uncommonly reported (0.4 %). Serious infusion reactions or hypersensitivity occurred in 0.4 % of patients treated with donanemab compared to 0.1 % on placebo.

All patients reporting infusion-related reactions had ADA. Higher ADA titre was associated with increased incidence of infusion-related reactions/immediate hypersensitivity events.

The majority of infusion reactions and hypersensitivity reactions have occurred within the first 4 doses of donanemab, although they can occur at any time. Treatment discontinuations in donanemab treated patients included IRR (3.5 %), hypersensitivity (0.6 %), and anaphylactic reaction (0.4 %), with no discontinuations due to these events in the placebo group.

Rechallenge led to subsequent IRR/hypersensitivity events in about 46.9 % of patients, with severity and type of symptoms usually similar to that of initial events.

Prophylactic medicines prior to subsequent infusions did not prevent IRR recurrence.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

4.9 Overdose

Single doses up to 40 mg/kg (approximately 2,800 mg in a 70 kg person) have been administered. ARIA-E occurred in 2 out of 4 patients administered this dose and resolved. In case of an overdose, MRI monitoring and supportive therapy may be initiated if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics, anti-dementia drugs ATC code: N06DX05

Mechanism of action

Donanemab is an immunoglobulin gamma 1 (IgG1) monoclonal antibody with high affinity for a modified, N-terminal truncated form of amyloid beta (N3pE Aβ). N3pE Aβ is present in brain amyloid plaques at low levels, and not detected in plasma and CSF. Donanemab binds to N3pE Aβ and aids plaque removal through microglial-mediated phagocytosis.

Pharmacodynamic effects

The percentage of donanemab treated patients who achieved amyloid clearance (that is, less than 24.1 Centiloids) in Study TRAILBLAZER-ALZ 2 was 32.5 % at week 24, 69.5 % at week 52 and 80.8 % at week 76 in the indicated population.

In study TRAILBLAZER-ALZ 2, the difference between donanemab and placebo in the change from baseline amyloid level at week 76 was statistically significant in the indicated population (- 89.24 Centiloids).

In Study TRAILBLAZER-ALZ 6, similar amyloid plaque reduction was observed at week 24 for the dosing regimen of 350/700/1 050 mg, then 1,400 mg every 4 weeks thereafter, when compared with the dosing regimen of 700 mg for the first three infusions, then 1,400 mg every 4 weeks thereafter, studied in the pivotal study.

Donanemab exposure decreased with increasing ADA titre. Amyloid beta reduction was found irrespective of ADA titre. No association was observed between the presence of ADA and outcomes on the iADRS and CDR-SB (see also section 4.4, 4.8 and 5.2).

Clinical efficacy and safety

Phase III Study TRAILBLAZER-ALZ 2
The safety and efficacy of donanemab were evaluated in a Phase III (TRAILBLAZER-ALZ 2) study. The study was double-blind placebo-controlled, parallel-group, in patients 60 to 85 years of age with early symptomatic AD (Mild Cognitive Impairment (MCI) due to AD or mild AD dementia, MMSE score 20 to 28 inclusive) and evidence of amyloid beta pathology confirmed by amyloid PET scan. The participants also had evidence of pathologic tau deposition on a flortaucipir PET scan.

In this study, 1,736 patients, were randomized 1:1 to receive 700 mg of donanemab every 4 weeks for the first 3 doses, and then 1,400 mg every 4 weeks via intravenous infusion (N = 860) or placebo (N = 876) for a total of up to 72 weeks. 1,447 (83.4 %) patients in the indicated population were randomised. Dosing was continued until study completion or amyloid plaque was cleared, defined as demonstrating a plaque level of less than 25 Centiloids for two consecutive amyloid PET scans or a single PET scan demonstrating a plaque level of less than 11 Centiloids. Additionally, dose suspension was allowed for treatment-emergent ARIA. If patients were already on symptomatic treatment (acetylcholinesterase inhibitors (AChEI) and/or the N-Methyl-D-aspartate inhibitor, memantine) at study entry, these treatments could continue. Symptomatic treatments could be added or changed during the study, at the investigator's discretion. The study excluded patients with pre-existing ARIA-E, greater than 4 microhaemorrhages, more than 1 area of superficial siderosis, any intracerebral haemorrhage > 1 cm or severe white matter disease.

At baseline, mean (SD) age was 73 (6.2) years, with a range of 59 to 86 years, with a mean (SD) baseline weight of 71.7 kg (15.7), with a gradual and progressive change in memory function for at least 6 months and with a mean (SD) Mini–Mental State Examination (MMSE) score of 22.29 (3.88). At baseline, 59.4 % had a MMSE score < 24. 57.4 % were female, 91.5 % were White, 5.7 % were of Hispanic or Latino ethnicity, 6.0 % were Asian, and 2.3 % were Black. Of the total number of patients randomized, 29 % were ApoE ε4 non-carriers, 54 % were heterozygotes, and 17 % were homozygotes. 55.6 % of patients were on AChEI, and 20.3 % on memantine. 61.0 % of patients were on either AChEI or memantine use. Mean (SD) of amyloid Centiloids at baseline was 102.5 (34.5). 68.2 % and 31.8 % were in the low-medium and high tau categories, respectively. A total of 24.7 % of patients discontinued treatment in the study. Of those, 29.3 % were patients in the donanemab arm and 20.1 % of patients in the placebo arm.

There were two primary analysis populations based on tau PET imaging at screening with flortaucipir: 1) low-medium tau level population, and 2) overall population (low-medium plus high tau level population).

The primary efficacy endpoint was change in cognition and function as measured by the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is an integrated assessment of cognition and daily function comprised of items from the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog_{13}: score range 0-85) and the Alzheimer's Disease Cooperative Study - instrumental Activities of Daily Living (ADCS-iADL: score range 0-59) scale, measuring the core domains across the AD clinical continuum. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance. Other efficacy endpoints included Clinical Dementia Rating Scale - Sum of Boxes (CDR-SB), ADAS-Cog_{13}, ADCS-iADL.

Important findings from the study for the indicated population in a post hoc analysis using a conservative method for the handling of missing data are presented in Table 4 below.

For the overall population, using the same conservative method, the difference between donanemab and placebo in the change from baseline in iADRS was 2.38 (95% CI: 0.985, 3.782), and in CDR-SB was -0.61 (95% CI: -0.850, -0.366). The effect was similar in the overall and the indicated restricted population.

Table 4: Efficacy analysis results of donanemab study TRAILBLAZER-ALZ 2 at week 76, in the indicated population (ApoE ε4 heterozygotes and non-carriers) using conservative method for handling of missing data[a]

Clinical Endpoint	ApoE ε4 heterozygotes and noncarriers	
	Dona N = 717	**Placebo N = 730**
iADRS (MMRM)		
Mean baseline (SD)	104.35 (14.23)	103.48 (14.23)
LS Mean change from baseline	-10.82	-13.47
Difference from placebo (95 % CI)	2.65 (1.04, 4.26)	
CDR-SB (MMRM)		
Mean baseline (SD)	3.97 (2.10)	3.98 (2.08)
LS Mean change from baseline	1.73	2.42
Difference from placebo (95 % CI)	-0.69 (-0.95, -0.43)	
ADAS-Cog_{13} (MMRM)		
Mean baseline (SD)	28.53 (8.88)	29.14 (8.98)
LS Mean change from baseline	5.67	7.03
Difference from placebo (95 % CI)	-1.35 (-2.19, -0.51)	
ADCS-iADL (MMRM)		
Mean baseline (SD)	47.84 (7.90)	47.65 (7.97)
LS Mean change from baseline	-4.91	-6.37
Difference from placebo (95 % CI)	1.46 (0.50, 2.42)	

Abbreviations: ApoE ε4 = allele subtype 4 of the gene coding for apolipoprotein Class E; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; CI = confidence interval; Dona=donanemab; iADRS = integrated Alzheimer's Disease Rating Scale; LS = Least-Square; MMRM = mixed model for repeated measures; N = number of participants; SD = standard deviation.

a Analyses performed in ITT (intent-to-treat) population that included all randomized participants; post hoc sensitivity analyses using conservative methods for handling missing data (multiple imputation with jump to reference and copy increments in reference).

Low-medium tau population
In the low-medium tau population (588 patients on donanemab vs 594 patients on placebo), using a conservative method for the handling of missing data, LS mean difference between donanemab and placebo was 3.15 (32.2 %) (95 % CI: 1.738, 4.557) on iADRS, and -0.61 (32.0 %) (95 % CI: -0.891, -0.330) on CDR-SB at Week 76.

High tau population
In a post-hoc analysis in the high-tau population, (271 patients on donanemab vs 281 patients on placebo), using a conservative method for the handling of missing data, LS mean difference between donanemab and placebo was 0.41 (2.1 %) (95 % CI: -2.518, 3.338) on iADRS, and -0.54 (16.0 %) (95 % CI: -1.014, -0.066) on CDR-SB at Week 76.

Phase III Study TRAILBLAZER-ALZ 6
The donanemab dosing regimen of 350/700/1,050 mg, followed by 1,400 mg every 4 weeks was evaluated in a Phase IIIb (TRAILBLAZER-ALZ 6) multicenter, randomized, double-blind, study in adults with early symptomatic AD (MCI due to AD or mild AD dementia, MMSE score 20 to 28 inclusive) and evidence of amyloid beta pathology confirmed by amyloid PET scan.

843 patients were randomized at a 1:1:1:1 ratio into four donanemab dosing regimens for a total of 72 weeks: 700 mg for the first three infusions, then 1,400 mg every 4 weeks thereafter (n=207), or one of the three alternative donanemab dosing regimens (including the dosing regimen: 350/700/1,050 mg, followed by 1,400 mg every 4 weeks; n=212), with the same total drug administered in all regimens.

The primary endpoint of the study was the proportion of participants with any occurrence of ARIA-E by week 24. The results showed that 14 % of patients receiving 350/700/1,050 mg, followed by 1,400 mg every 4 weeks, compared with 24 % receiving 700/700/700 mg, followed by 1,400 mg every 4 weeks, experienced ARIA-E by week 24, a 41 % lower relative risk. Similar amyloid plaque reductions were seen at 24 weeks in all dosing regimens.

5.2 Pharmacokinetic properties

Absorption

Donanemab is for intravenous administration only.

Distribution

Following intravenous dosing, donanemab undergoes biphasic elimination. The central volume of distribution is 3.36 L with 18.7 % inter-individual variability. Peripheral volume of distribution is 4.83 L, with 93.9 % inter-individual variability. In a clinical pharmacology study, the ratio of cerebrospinal fluid to serum concentration was observed at approximately 0.2 %.

Biotransformation

Donanemab is a monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as an endogenous IgG, hence there is no metabolic inhibition or induction of enzymatic pathways. Donanemab is not expected to be metabolized by the cytochrome P450 families of drug-metabolizing enzymes responsible for metabolism and elimination of small molecules and would, therefore, not produce any active metabolites.

Elimination

The half-life of donanemab is approximately 12.1 days. Donanemab clearance was 0.0255 L/h (24.9 % inter-individual variability).

Linearity/non-linearity

Donanemab showed dose proportional increase and time linearity in serum exposure in dose range 350 mg to1,400 mg.

Other intrinsic factors

The PK of donanemab was not affected by age (54-88), sex (55.0 % female), or race (89.9 % White, 6.3 % Asian, 2.9 % Black and 0.3 % American Indian or Other), based on a population PK analysis. While body weight (range 39 to 157 kg, mean of 74 kg) was found to influence both clearance and volume of distribution, the resulting changes do not suggest a need for dose adjustment.

Immunogenicity

Donanemab clearance increased linearly with log (ADA titre). This increase in clearance with titre resulted in a 17 % decrease in $AUC_{\tau,ss}$, and a 31 % decrease in drug concentration before the next dose ($C_{trough,ss}$) (see sections 4.4 and 5.1). Although donanemab exposure decreased with increasing ADA titer, the development of ADA was not associated with loss of clinical efficacy of donanemab.

Renal and hepatic impairment

Renal and hepatic impairment did not affect the PK of donanemab based on population PK analysis. No dose adjustment is necessary in patients with renal or hepatic impairments.

Pharmacokinetic/pharmacodynamic relationships

Model based exposure-response analyses demonstrated that donanemab treatment was associated with a reduction in clinical decline on iADRS and CDR-SB. An association between reduction in amyloid beta plaque from baseline and clinical decline on iADRS and CDR-SB was also observed.

In addition, model based association between donanemab treatment and ARIA-E was demonstrated and identified risk factors such as ApoE ε4 genotype, number of baseline microhaemorrhages and presence of superficial siderosis at baseline.

During an off-treatment period, amyloid PET values began to increase with a median rate of 2.80 Centiloids/year.

In single doses from 350 to 2,800 mg (approximately 2 times the dosage of 1,400 mg for 70 kg of body weight studied in the pivotal study), and multiple 350 to 1,400 mg doses, exposures (C_{max} and AUC) increased proportionally. Similar exposure was observed for the donanemab dosing regimen of 350/700/1,050 mg, then 1,400 mg every 4 weeks thereafter, compared with the dosing regimen of 700 mg for the first three infusions, then 1,400 mg every 4 weeks thereafter, that established clinical efficacy in the pivotal study.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity. No animal studies have been performed to test donanemab for potential of carcinogenicity, genotoxicity, reproductive toxicity or fertility impairment.

A weight-of-evidence assessment of all data, including evaluation of the target biology (residing in deposited Aβ plaques only), the nature of the product (high specificity of the monoclonal antibody molecule for the target and composition of naturally occurring amino acids and monosaccharides), the mechanism of action (phagocytic removal of amyloid plaque in the CNS) and the lack of effects in the toxicology studies, suggest a low potential for risk of reproductive toxicity or carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium citrate dihydrate
Citric acid anhydrous
Polysorbate 80
Water for injection

6.2 Incompatibilities

Kisunla contains polysorbate 80. Polysorbates are known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). Materials used for the preparation and administration of donanemab dosing solution should be DEHP-free.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Unopened vial

Store in a refrigerator (2°C to 8°C) until time of use.
May be stored unrefrigerated for up to 3 days at room temperature (up to 25°C).
Keep the vial in the outer carton in order to protect from light.
Do not freeze or shake.

Diluted solution for infusion

Use prepared dosing solution immediately.
If not used immediately, store the donanemab dosing solution in a refrigerator (2°C to 8°C) for up to 72 hours or for up to 12 hours at room temperature (up to 25°C) assuming dilution has taken place using aseptic techniques.
Storage times include the duration of infusion.
Do not freeze the donanemab dosing solution.

6.5 Nature and contents of container

Kisunla is supplied in a type I clear glass, 20 mL, single dose vial, with a chlorobutyl elastomer stopper and an aluminium seal with a polypropylene cap, individually packaged in a carton.
Pack sizes of 1 vial.

6.6 Special precautions for disposal and other handling

Kisunla contains polysorbate 80; therefore, appropriate materials for preparation and administration must be used (see section 6.2). Donanemab solution for infusion should be prepared and administered by a qualified healthcare professional using aseptic technique:

Allow donanemab to equilibrate to room temperature for approximately 30 minutes before preparation.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use donanemab if it is cloudy or there are visible particles.

After dilution and preparation in sodium chloride 9 mg/mL (0.9 %) solution for injection (see Table 5), donanemab is administered as an intravenous infusion.

Table 5: Preparation of donanemab

Kisunla Dose (mg)	Kisunla Volume (mL)	Volume of sodium chloride 9 mg/mL (0.9 %) solution for injection (mL)	Final volume of diluted solution to be infused (mL)	Final concentration of diluted solution (mg/mL)[a]
350 mg	20 mL	15 mL to 67.5 mL	35 mL to 87.5 mL	350 mg/87.5 mL (4 mg/mL) to 350 mg/35 mL (10 mg/mL)
700 mg	40 mL[b]	30 mL to 135 mL	70 mL to 175 mL	700 mg/175 mL (4 mg/mL) to 700 mg/70 mL (10 mg/mL)
1,050 mg	60 mL[c]	45 mL to 202.5 mL	105 mL to 262.5 mL	1,050 mg/262.5 mL (4 mg/mL) to 1,050 mg/105 mL (10 mg/mL)
1,400 mg	80 mL[d]	60 mL to 270 mL	140 mL to 350 mL	1,400 mg/350 mL (4 mg/mL) to 1,400 mg/140 mL (10 mg/mL)

[a] final concentration of 4 mg/mL to 10 mg/mL
[b] 2 vials of Kisunla
[c] 3 vials of Kisunla
[d] 4 vials of Kisunla

Gently invert the infusion bag to mix.

Administer diluted solution over a period of at least 30 minutes. Administer the entire infusion solution.

Flush the line with sodium chloride 9 mg/mL (0.9 %) solution for injection at the end of the infusion.

Observe the patient post-infusion for a minimum of 30 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER

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