CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761269
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Reviewer Name(s)	Carla Darling, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 16, 2022
Subject	Evaluation of Need for a REMS
Established Name	Lecanemab-irmb
Trade Name	Leqembi
Name of Applicant	Eisai Inc.
Therapeutic Class	Anti-Amyloid Beta Monoclonal Antibody
Formulation(s)	Solution for Injection
Dosing Regimen	10 mg/kg administered by intravenous infusion every 2 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Leqembi (lecanemab-irmb) is necessary to ensure the benefits outweigh its risks. Eisai, Incorporated submitted a Biologic Licensing Application (BLA) 761269 for lecanemab-irmb (lecanemab), an amyloid beta directed antibody with the proposed indication for the treatment of Alzheimer's Disease. Lecanemab was reviewed under the accelerated approval pathway. The applicant did not submit a proposed REMS or risk management plan with this application.

Alzheimer's Disease (AD) is a progressive, degenerative neurologic disorder characterized by progressive memory loss, behavioral problems, and inability to perform activities of daily living.[1] AD is the most common cause of dementia and a leading cause of morbidity and mortality in the aging population.[1,2] As there are no approved treatments designed to cure the disease, there remains an unmet need for treatment options for AD.

DRM and the Division of Neurology 1 (DN1) have determined that a REMS is not needed to ensure the benefits of lecanemab outweigh its risks. The efficacy of lecanemab was evaluated in one pivotal phase 2 trial. The clinical reviewer determined that the applicant provided substantial evidence of effectiveness based on the effect of lecanemab on brain amyloid, which is likely to predict clinical benefit in AD.[3] As such, lecanemab meets the accelerated approval criteria by having the potential to address an unmet need in a serious disease and by decreasing brain beta-amyloid plaques to likely achieve clinical benefit.

Based on the safety and efficacy information available, a REMS is not necessary to ensure the benefits outweigh the risk. The risks associated with lecanemab include amyloid related imaging abnormalities (ARIA), including ARIA-edema (ARIA-E) and ARIA-hemosiderin deposition (ARIA-H) and infusion reactions. Another anti-amyloid beta monoclonal antibody, Aduhelm (aducanumab), was approved on June 7, 2021 without a REMS and shares similar risks;[4] therefore, prescribers are likely aware of the risks and appropriate monitoring and management. The risks of ARIA and other infusion reactions will be included in the Warnings and Precautions section of the prescribing information. Labeling will convey the risks of infusion reactions and ARIA and include recommendations for MRI monitoring, radiographic classification criteria for ARIA severity, the need for assessment of symptoms associated with ARIA throughout treatment, and considerations for continuing lecanemab in the setting of ARIA. A Medication Guide will communicate the risks to patients and caregivers. At the time of this review, final labeling, and post-marketing requirements (PMRs) were still under negotiation. However, the accelerated approval pathway requires a confirmatory study, and we anticipate post-marketing requirements as well as enhanced pharmacovigilance for the risk of ARIA. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Leqembi (lecanemab) is necessary to ensure the benefits outweigh its risks. Eisai Inc. (Applicant) submitted a Biologic Licensing Application (BLA) 761269 for lecanemab with the proposed indication for the treatment of Alzheimer's Disease (AD).[5] This application is under review in the Division of Neurology 1 under the accelerated approval pathway. This indication is eligible for the accelerated approval pathway based on the reduction in brain amyloid beta plaques observed in patients treated with lecanemab. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Lecanemab, a new molecular entity (NME),[a] is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody (mAb) directed against aggregated soluble and insoluble forms of amyloid beta.[6] A defining pathophysiology of AD includes accumulation of amyloid beta (Aβ) plaques in the brain. Lecanemab reduces amyloid in the brain of people with AD.[7] It is theorized that lecanemab's effect on both soluble aggregated forms of Aβ and amyloid plaques will attenuate the pathological course of AD and thereby slow disease progression.[5]

Lecanemab is proposed as a 10 mg/kg intravenous infusion administered every 2 weeks.[5] Lecanemab is not currently approved in any jurisdiction.[8] Lecanemab is intended as a chronic therapy.[b] Lecanemab will most likely be administered in health care supervised settings, such as infusion centers and provider clinics/offices. Lecanemab was granted breakthrough therapy designation, fast track designation, priority review, and is being reviewed under the accelerated approval pathway. If approved, lecanemab would be the second anti-amyloid antibody approved under the accelerated approval pathway for the treatment of AD.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761269 relevant to this review:

- 06/21/2021: Breakthrough therapy designation granted
- 09/23/2021: Rolling review request granted
- 12/20/2021: Fast track designation granted
- 05/06/2022: Final portion of rolling original BLA received

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 07/01/2022: Priority review request granted
- 11/10/2022: A Late cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no issues related to risk management have been identified to date that require a REMS for lecanemab

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

AD is a progressive, degenerative neurologic disorder characterized by progressive memory loss, behavioral problems, and inability to perform activities of daily living.[1] AD is the most common cause of dementia and a leading cause of morbidity and mortality in the aging population.[1,2] About 6.5 million people who are age 65 and older in the United States (US) suffer from AD.[2,c] Without interventions to prevent or slow the disease, it has been projected that this number could increase to 12.7 million by 2050[2]. AD is currently the seventh leading cause of death in the US and the fifth leading cause of death for people ages 65 and older.[2,9,d]

The clinical course of the disease is a continuum of preclinical disease, mild cognitive impairment, and dementia.[1,2] Early in the disease, changes may be undetectable in affected patients but progress to subtle problems with memory and thinking, and ultimately difficulties with memory, language, and problem-solving, which limit the individual's ability to perform everyday activities. Patients suffering from AD experience significant morbidity while living with the disease due to progressive memory loss, behavioral problems, and loss of independence due to inability to perform activities of daily living. The burden associated with AD is significant due to high direct medical costs as well as the unpaid time family may spend caring for those suffering with the disease.[2] Life expectancy may vary depending on several factors, however, the average survival is 4-8 years after a diagnosis.[1,10]

3.2. Description of Current Treatment Options

There are currently no therapies that cure or slow the clinical decline of AD.[11] Current treatment goals are aimed at maintaining quality of life, treatment of cognitive symptoms, and management of behavioral and psychological symptoms of dementia.[2] Available FDA approved drugs are cholinesterase inhibitors (e.g. donepezil, rivastigmine, and galantamine) for the treatment of mild, moderate, and severe AD dementia; N-methyl-D-aspartate antagonist, memantine, for the treatment of moderate to severe AD dementia; and aducanumab for the treatment of AD in patients with mild cognitive

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

impairment or mild dementia.[11] Cholinesterase inhibitors and memantine only provide symptomatic benefits and are less beneficial as the disease progresses.[11]

Aducanumab was the first FDA approved treatment that targets the underlying pathophysiological changes associated with AD.[12] Under the accelerated approval pathway, aducanumab was approved based on reduction in amyloid beta plaques to likely achieve clinical benefit. Continued approval for this indication is contingent upon verification of clinical benefit in confirmatory trials. The key risk associated with aducanumab is amyloid related imaging abnormalities (ARIA), including ARIA-edema (ARIA-E) and ARIA-hemosiderin deposition (ARIA-H). There is a need for disease-modifying therapies that can slow progression, prolong independence, and maintain quality of life. See Table 1 in Appendix 10.2 for a list of currently approved FDA treatments.

4. Benefit Assessment

The efficacy of lecanemab in AD was evaluated in one pivotal phase 2 trial, Study BAN2401-G000-201 (NCT01767311), henceforth referred to as study 201. Study 201 consisted of a multinational, multicenter, double-blind, placebo-controlled, parallel-group, dose finding study. Using a Bayesian design with response-adaptive randomization (RAR), the study evaluated lecanemab in 856 patients (lecanemab group=609, placebo group=247) with early AD (patients with confirmed amyloid pathology and mild cognitive impairment [64%] or mild dementia state of disease [36%]). The study was designed to determine the most efficacious dose regimen of lecanemab and included an 18-month treatment period, followed by a gap period (off lecanemab) for 9 to 58 months, and an ongoing open label extension (OLE) period. Patients in the lecanemab group received either 2.5, 5, or 10 mg/kg given biweekly, or 5 or 10 mg/kg given every 4 weeks. During the OLE, all patients received lecanemab 10 mg/kg biweekly. In the earlier part of the placebo-controlled period of study 201, the study protocol was amended to stop further enrollment of apolipoprotein e4 variant (APOE ε4) carriers to the proposed dose group (lecanemab 10mg/kg biweekly) and those who were on this dose for 6 months or less were to be discontinued (see Section 5.2.2 for further details).

The primary endpoint was change from baseline score on Alzheimer's Disease Composite Score (ADCOMS) at 12 months with a threshold of 80% probability of greater than 25% clinical reduction in decline compared to placebo. The lecanemab 10 mg/kg biweekly treatment group was identified by the Applicant as the most efficacious dose regimen on ADCOMS at 12 months; however, the primary endpoint was not met. Results show that lecanemab 10mg/kg biweekly had 64% probability to be better than placebo by achieving a 25% clinical reduction in decline, which did not meet the prespecified primary endpoint threshold. Additional, secondary endpoints include change from baseline at 18 months in amyloid positron emission tomography (PET), ADCOMS, clinical dementia rating scale - sum of boxes (CDR-SB) and Alzheimer's Disease Assessment Scale - Cognitive Subscale containing 14 tasks (ADAS-Cog14). Three of the four secondary endpoints showed statistically significant differences at 18 months in the lecanemab 10mg/kg biweekly group compared to placebo including a reduction from baseline in amyloid plaque with a mean difference of -73.5 Centiloids ($p<0.001$) as well as less decline in ADCOMS score and less decline in ADAS-Cog14.[6]

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on the effect of lecanemab on brain amyloid plaques, which is likely to predict clinical benefit in AD and supports accelerated approval.[e,12] The reviewer concluded: "Lecanemab treatment results in a robust and statistically significant reduction in brain amyloid plaque with a magnitude that the Division has concluded to be reasonably likely to predict clinical benefit."[3] Changes in the surrogate endpoint of brain amyloid have been determined by the Agency to be reasonably likely to predict clinical benefit based on the approval of aducanumab, another anti-amyloid beta monoclonal antibody.[4,12,13]

5. Risk Assessment & Safe-Use Conditions

The safety database includes 763 patients exposed to lecanemab at any dose including 654 patients from study 201 who received at least one dose of lecanemab (609 patients from the placebo controlled period and 45 patients from the placebo group that were exposed to lecanemab for the first time in the OLE), and 255 patients who received at least one dose of the proposed dose of 10 mg/kg biweekly.[14]

The most common adverse reactions at the proposed dose included infusion-relates reactions, ARIA-E, headache, cough, diarrhea, atrial fibrillation, hematuria, paresthesia, dental caries, and lymphopenia.[14] The clinical safety reviewer notes that the safety of lecanemab in patients with moderate or severe dementia is unknown as these patients were excluded from the key studies analyzed for review of safety.[14] It is also important that the trial protocol was amended early in study 201 to mitigate the risk of ARIA as required by the European Health Authorities. The study protocol was amended to stop further enrollment and allow discontinuation of APOE ε4 carriers, which resulted in fewer APOE ε4 carriers in the proposed dose group of lecanemab 10 mg/kg biweekly compared to other study arms. Therefore, the smaller sample size of APOE ε4 carriers in the proposed dose of lecanemab 10 mg/kg biweekly is an important limitation in the safety analysis of ARIA.

Infusion-related reactions and ARIA were adverse events of special interest and discussed in more depth below (see Section 5.2).

5.1. Serious Adverse Events[f]

5.1.1. Deaths

There were 24 deaths in the lecanemab clinical development program as of a data cutoff date of 31 December 2021 (120-Day Update). Twelve (12) deaths occurred in study 201 including 7 deaths in the

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

placebo-controlled period and 5 deaths in the OLE period. An additional twelve (12) deaths occurred in the ongoing Phase 3 study, BAN2401-G000-301 (NCT03887455) also referred to as study 301, including 9 deaths in the placebo-controlled period and 3 deaths in the OLE.

In the placebo-controlled period of study 201, there were a total of 7 deaths with 5 deaths in the lecanemab exposed group and 2 deaths in the placebo group. One death in the lecanemab exposed group was attributed to brain neoplasm with surrounding vasogenic edema, which occurred in a patient treated with lecanemab 2.5mg/kg biweekly and was considered possibly related to drug by the investigator. Causes of death in the other four lecanemab exposed patients included cardiac arrest, multiple organ dysfunction syndrome, spinal cord injury and respiratory failure. None of the cases were preceded by ARIA.

In the open-label period of study 201, there were 5 reported deaths. Causes of death included cervical vertebral fracture secondary to a motor vehicle accident, COVID-19 pneumonia, Alzheimer's dementia, and malignancy (2). None of the cases were preceded by ARIA but most could not be ruled out as unrelated to the study drug.

In ongoing study 301, 9 deaths occurred in the placebo-controlled period, which remains blinded to treatment assignment and 3 deaths occurred in the OLE phase. Of these 12 deaths, there was one death [redacted] (b) (6) in a patient receiving blinded study drug, which was due to a cerebral hemorrhage (> 1cm). This patient had isolated cerebral hemorrhage later during treatment (after the 25th and 26th dose) and did not have ARIA-E or ARIA-H at the time of the cerebral hemorrhage. The clinical reviewer concluded that the role of lecanemab cannot be ruled out in the occurrence of intracranial hemorrhage and related death since it is unclear from the narrative whether the participant may have had other ARIA events prior to the 26th dose that have not been considered serious AEs. Other causes of death include: cerebrovascular infarction (1), myocardial infarction (3), COVID-19 infection (4), pancreatic cancer (1), acute respiratory failure (1), and acute cardiac failure (1).

The agency became aware of two additional deaths [redacted] (b) (6) due to one or more cerebral hemorrhages > 1cm while participating in study 301 OLE.[14] Both patients initially received placebo during the placebo-controlled period of study 301 and in the OLE received lecanemab and concomitant antithrombotic or thrombolytic medication. One patient [redacted] (b) (6) received apixaban and thrombin prior to the cerebral hemorrhage and the other patient [redacted] (b) (6) received alteplase (tPA) for an acute stroke and sustained bilateral multiple hemorrhages and a subarachnoid bleed, which led to death. The clinical reviewer concluded that no firm conclusions could be made on whether the risk of ARIA-H or cerebral hemorrhage while on lecanemab and a concomitant antithrombotic is higher than the risk while on antithrombotic alone.[14]

Overall, the clinical safety reviewer concluded that based on the review of death narratives, none of the deaths seem to be directly related to study drug or due to complications of ARIA; however in many of the cases the relation to lecanemab could not be ruled out.[14]

5.2. Adverse Event of Special Interest (AESI)

5.2.1. Infusion-Related Reactions

In the placebo-controlled period of study 201, infusion-related reactions were observed in 19.9% of patients treated with lecanemab 10mg/kg biweekly versus 3% on placebo.[14,g] Most infusion-related reactions were reported as mild (56%) or moderate (44%) and 76% of infusion reactions were classified as Grade 1 or 2. Infusion-related reactions were observed in patients despite patients receiving medications to prevent reactions. Infusion-related reactions that lead to drug discontinuation were observed in 2.5% of patients treated with lecanemab 10 mg/kg biweekly versus 0.8% in the placebo group. No participant experienced an anaphylactic reaction.

In the placebo-controlled period of study 201, one subject in the lecanemab 10 mg/kg biweekly group was hospitalized after the second dose of study drug due to a reported infusion-related reaction with vomiting, dizziness, chills, and fever (38.5°C). The study drug was permanently discontinued due to the event of infusion related reaction.

The clinical safety reviewer recommends communicating the risk of infusion related reactions in Section 5, Warnings and Precautions of the prescribing information and in the Medication Guide.[14]

5.2.2. Amyloid Related Imaging Abnormalities (ARIA)

Spontaneous ARIA-E in patients with or without AD is rare.[15,16] Based on observations from aducanumab and studies in other monoclonal antibodies, the risk for ARIA-E is higher at treatment initiation, in APOE e4 carriers, and with higher dosage.[17] ARIA-H can present on MRI as cerebral microhemorrhages, hemosiderosis, or cerebral hemorrhages.[17] Additionally, spontaneous microhemorrhages overall have a prevalence of ~5% in the elderly with higher prevalence in those with cerebrovascular risk factors.[18]

Similar to other anti-amyloid beta monoclonal antibodies, a higher incidence of ARIA was observed in lecanemab treated patients compared to placebo.[h] During the placebo-controlled period of study 201, ARIA monitoring with safety MRIs was conducted during screening, prior to the 4th (European sites only), 5th, 7th, 14th, 20th, 27th, and 33rd infusion, and 2 weeks after the last dose of study drug. During the placebo-controlled period of study 201, dosing was discontinued for any patient with symptomatic ARIA-E regardless of the radiographic severity of ARIA-E. ARIA (-E and/or -H) was observed in 12% of patients treated with lecanemab 10 mg/kg biweekly compared to 5% of patients on placebo.

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[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

ARIA-E was observed in 10% of patients treated with lecanemab 10 mg/kg biweekly in the placebo-controlled period of study 201, compared to 1% of patients on placebo. The maximum radiographic severity of ARIA-E in patients treated with lecanemab 10 mg/kg biweekly was mild in 7 patients (44%), moderate in 7 patients (44%), and severe in 2 patients (12%). Most ARIA-E (75%) occurred within the first 7 doses. Additionally, ARIA-E radiographically resolved in 62% of these patients by 12 weeks and 81% by 21 weeks. There were no deaths due to ARIA-E in the placebo-controlled period or in the OLE.

In placebo-controlled period of study 201, ARIA-H was observed in 6% of patients treated with lecanemab 10 mg/kg biweekly compared to 5% of patients on placebo. The radiographic severity of most ARIA-H was classified as mild; severe ARIA-H microhemorrhage occurred in 1% of patients with ARIA-H microhemorrhage. In patients treated with lecanemab 10 mg/kg biweekly, there was a higher incidence of ARIA-H (microhemorrhage and superficial siderosis) in those receiving antithrombotics (antiplatelets or anticoagulants) compared to those not receiving antithrombotics, 6% compared to 4%, respectively. A similar difference was observed in the OLE period in patients treated with lecanemab 10 mg/kg biweekly where ARIA-H was observed in 17% of patients receiving antithrombotics compared to 9% in those who were not.

In the placebo-controlled period of study 201, 25% of patients with ARIA (-E and/or -H) treated with lecanemab 10 mg/kg biweekly had at least 1 treatment emergent clinical symptom present compared to 0% of patients on placebo. In patients treated with lecanemab 10 mg/kg biweekly, the most common symptoms reported in patients with ARIA includes headache, confusion or altered mental status, visual disturbance, and agitation. One possible seizure was reported but could not be confirmed by the sponsor.

Similar to other anti-amyloid beta monoclonal antibodies, a higher incidence of ARIA-E was observed in APOE ε4 carriers treated with lecanemab. In the placebo-controlled period, ARIA-E occurred more frequently in patients treated with lecanemab 10 mg/kg biweekly that were APOE ε4 homozygotes compared to heterozygotes and noncarriers (50 % in homozygotes, 5% in heterozygotes and 8 % in noncarriers). APOE ε4 homozygotes also had an increased frequency of ARIA-H microhemorrhage (30 % in homozygotes, 8 % in heterozygotes, and 3 % in noncarriers). Notably, there were fewer APOE ε4 carriers in the proposed dose group of lecanemab 10 mg/kg biweekly (30 %), compared to 69-89 % in other study arms, and ~30-70 % in individuals with AD in the general population. The smaller sample size of APOE ε4 carriers in the proposed dose group (lecanemab 10 mg/kg biweekly) was a result of the study protocol amendment to stop further enrollment and allow discontinuation of patients who were APOE ε4 carriers. While the small subset of APOE ε4 carriers in the proposed dose of lecanemab 10 mg/kg biweekly may impact the extent of the risk of ARIA in this subgroup, the risk of ARIA is still observed in these patients as evidenced by a higher incidence of ARIA (-E or -H) in homozygotes.

The clinical safety reviewer recommends communicating the risk of ARIA in Section 5, Warnings and Precautions of the prescribing information and in the Medication Guide.[14] Additionally, the clinical reviewer recommends including guidance regarding monitoring and implications regarding a finding of ARIA on subsequent dosing in Section 2.3 and 2.4 of the prescribing information as well as including a statement that the use of antithrombotic or thrombolytic medications may increase risk of ARIA-H or

cerebral hemorrhage in those treated with lecanemab. The clinical reviewer notes uncertainties with the optimal timing and frequency of MRI monitoring, characterization of ARIA in APOE-ε4 carriers, safety of concomitant use of medications that increase bleeding risk, safety of treating AD patients with co-morbid cerebral amyloid angiopathy, as well as the safety of treating patients through episodes of radiographically mild ARIA-E with mild clinical symptoms or through episodes of asymptomatic radiographically mild ARIA-H, therefore, recommends enhanced post marketing pharmacovigilance for ARIA-E and ARIA-H aimed to further characterize the safety of lecanemab.

6. Expected Postmarket Use

The anticipated prescribing population for lecanemab will likely be memory disorder specialists which include neurologists, psychiatrists, and geriatricians, who should have experience in the care for patients with AD. Lecanemab will likely be administered in healthcare supervised settings, such as infusion centers and provider clinics/offices. As lecanemab will require brain MRI evaluation prior to treatment initiation and during therapy, radiologists will be involved in care to identify ARIA and classify radiographic severity. Memory disorder clinics likely include a multi-disciplinary team of specialists and may include neuroradiologists with specialized expertise. Memory disorder specialists and neuroradiologists may be aware of the risk of ARIA since ARIA has been observed in clinical trials with other anti-amyloid beta monoclonal antibodies including aducanumab, which received accelerated approval in June 2021.[13,19]

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for lecanemab beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewers recommend accelerated approval of lecanemab based on reduction in brain amyloid plaque to likely achieve clinical benefit.[3]

AD is a progressive, degenerative neurologic disorder characterized by progressive memory loss, behavioral problems, and inability to perform activities of daily living.[1] AD is the most common cause of dementia and a leading cause of morbidity and mortality in the aging population. Most options target symptoms of AD except for aducanumab, which was the first FDA approved treatment that targets the underlying pathophysiology associated with AD. Aducanumab, received accelerated approval based on reduction in amyloid beta plaques to likely achieve clinical benefit and continued approval for this indication is contingent upon verification of clinical benefit in ongoing confirmatory trials.

As there are no approved treatments designed to cure the disease, there remains an unmet need for treatment options for AD. Lecanemab offers an additional anti-amyloid beta monoclonal antibody option for the treatment of AD. The use of lecanemab in AD resulted in statistically significant decreases from baseline in brain amyloid plaque. The Division of Neurology 1 determined that there is substantial

evidence that lecanemab reduces amyloid beta plaques in the brain and that the reduction in these plaques is reasonably likely to predict clinical benefit.

Lecanemab is associated with increased risk of ARIA (-E and/or -H), which has also been observed in clinical development programs for aducanumab as well as other investigational anti-amyloid antibodies. The majority of ARIA is asymptomatic and usually mild or moderate in severity. In most cases, ARIA resolved radiographically and symptomatically over time after detection. ARIA can be detected by MRI and managed with close MRI monitoring and dose adjustments.

Prescribers are likely to be familiar with the risk of ARIA as the risk of adverse events (including ARIA) is well documented for the approved anti-amyloid beta monoclonal antibody, aducanumab and the risk of ARIA is also described in published expert recommendations on appropriate use for aducanumab.[4,17,19] Additionally, the risk of ARIA will be communicated through Section 5: Warnings and Precautions and in the Medication Guide.[6] At the time of this review, final labeling and PMRs were still under negotiation. Labeling is expected to convey the risk of ARIA and include recommendations for MRI monitoring, radiographic classification criteria for ARIA severity, the need for assessment of symptoms associated with ARIA throughout treatment, and considerations for continuing lecanemab in the setting of ARIA. Given that the accelerated approval pathway requires confirmatory trials and the clinical reviewer recommends enhanced post-market pharmacovigilance for the risk of ARIA, there should be additional data on the safety of lecanemab in a real-world setting.[14] If new safety information becomes available, DRM can re-evaluate the need for a REMS

The applicant voluntarily proposed an educational plan to address the risk of ARIA and infusion reactions. The proposed educational plan includes educational materials for prescribers, radiologists and patients that will be made available via a website. DRM does not object the to the proposed voluntary activities; however, as these materials are not part of labeling or a REMS, they should be reviewed by the Office of Prescription Drug Promotion.

Overall, the clinical reviewer concludes the safety profile of lecanemab is acceptable. Based on the data available, the seriousness of the disease state, and the prescribing community's likely familiarity with the risks associated with lecanemab that do not pose unique REMS considerations compared with the risks associated with other therapies, this reviewer has concluded that should lecanemab be approved, a REMS is not necessary to ensure the benefits outweigh the risks of lecanemab.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The side effect profile is similar to other anti-amyloid beta monoclonal antibodies including the risk of ARIA and prescribers are likely to be familiar with and able to appropriately monitor for the risks. At the time of this review, the labeling and PMR negotiations were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the Division of Neurology 1 have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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10.2. Table 1. Drugs Approved in the US for Alzheimer's Disease

Name (generic); Approval Year	Indication	Formulation(s)	Safety and Tolerability Issues	Risk Management Approaches
Aricept; Aricept ODT (donepezil hydrochloride); 1996	Treatment of dementia of the Alzheimer's type; efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's disease	Oral tablets, oral disintegrating tablets	Safety issues related to increased cholinergic activity including the following: may exaggerate the effects of succinylcholine-type muscle relaxation during anesthesia; cardiac effects (bradycardia, heart block, syncopal episodes); peptic ulcer disease and gastrointestinal (GI) bleeding; nausea and vomiting; weight loss; bladder outflow obstruction; seizures; respiratory adverse events (caution in patients with pulmonary conditions)	Labeling – Warning and Precaution
Exelon (rivastigmine tartrate; rivastigmine transdermal system); 2000	Mild, moderate, and severe dementia of the Alzheimer's type and mild-to-moderate dementia associated with Parkinson's disease (PD)	Oral capsules; oral solution; transdermal patch	Significant gastrointestinal adverse reactions (nausea, vomiting, decreased appetite, weight loss, dehydration); allergic dermatitis; risks due to increased cholinergic activity (same as donepezil above); impairment in driving or use of machinery Patch also includes hospitalization and rarely death due to application of multiple patches at the same time; skin application site reactions	Labeling – Warning and Precaution
Razadyne; Razadyne ER (galantamine hydrobromide); 2001	Treatment of mild to moderate dementia of the Alzheimer's type	Oral immediate release and extended-release capsules; oral solution	Serious skin reactions (Stevens Johnson syndrome and acute generalized exanthematous pustulosis), risks due to increased cholinergic activity (same as donepezil above); deaths in subjects with mild cognitive	Labeling – Warning and Precaution

			impairment in two randomized trials	
Namenda, Namenda XR (memantine hydrochloride); 2003	Treatment of moderate to severe dementia of the Alzheimer's type	Oral tablets; oral extended-release capsules	Genitourinary conditions (decreased urinary elimination of memantine with conditions that increase urinary pH)	Labeling – Warning and Precaution
Namzaric (memantine and donepezil hydrochloride); 2014	Treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily	Oral extended-release capsules	Labeled safety issues are outlined for donepezil and memantine above	Labeling – Warning and Precautions
Aduhelm (aducanumab-avwa); 2021	Treatment of Alzheimer's disease; should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials	Intravenous infusion	Amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis	Labeling – Warning and Precautions

Source: Information obtained from labeling from Drugs@FDA

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