CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 12, 2022
To:	E. Andrew Papanastasiou, Regulatory Project Manager **Division of Neurology I (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samuel Fasanmi, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	LEQEMBI (lecanemab-irmb)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761269
Applicant:	Eisai, Inc.

1 INTRODUCTION

On September 27, 2021, Eisai, Inc., submitted for the Agency's review a rolling submission of an Original New Biologic License Application (BLA) # 761269 for LEQEMBI (lecanemab-irmb) injection, for intravenous use. The purpose of this application is to seek approval for the use of LEQEMBI (lecanemab-irmb) injection, for intravenous use to treat early Alzheimer's disease (EAD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on January 5, 2022, for DMPP and on November 17, 2022, for OPDP to review the Applicant's proposed Medication Guide (MG) for LEQEMBI (lecanemab-irmb) injection, for intraenous use.

2 MATERIAL REVIEWED

- Draft LEQEMBI (lecanemab-irmb) MG received on September 27, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on December 5, 2022, and OPDP on December 2, 2022.
- Draft LEQEMBI (lecanemab-irmb) Prescribing Information (PI) received on September 27, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on December 5, 2022, and OPDP on December 2, 2022.
- Approved ADUHELM comparator labeling dated April 24, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of lecanemab-irmb (LEQEMBI) BLA 761269 MG

SAMUEL A FASANMI
12/13/2022 09:53:01 AM

MARCIA B WILLIAMS
12/13/2022 09:56:26 AM

LASHAWN M GRIFFITHS
12/13/2022 10:01:44 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 12/12/2022

To: Deniz Erten-Lyons/Clinical Reviewer, M.D.
Division of Neurology Products (DN1)

E. Andrew Papanastasiou, Regulatory Project Manager, (DN1)

Tracy Peters, Associate Director for Labeling, (DN I/II)

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for Leqembi (lecanemab-irmb) injection, for intravenous use

BLA: 761269

In response to DN1 consult request dated November 17, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for Leqembi (lecanemab-irmb) injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 on December 02, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 26, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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/s/

SAMUEL A FASANMI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 7, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761269
Product Name and Strength:	Leqembi (lecanemab-irmb) Injection, 200 mg/2 mL (100 mg/mL) and 500 mg/5 mL (100 mg/mL)
Applicant/Sponsor Name:	Eisai Inc.
OSE RCM #:	2022-88-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling and responses to recommendations that we made during a previous label and labeling review[a] received on September 26, 2022 for Leqembi. The Division of Neurology 1 (DN 1) requested that we review the revised container labels and carton labeling for Leqembi (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Weitzman B. Label and Labeling Review for Leqembi (BLA 761269). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 AUG 19. RCM No.: 2022-88.

APPENDIX A. RESPONSES TO OUR RECOMMENDATIONS AND IMAGES OF LABELS AND LABELING RECEIVED ON SEPTEMBER 26, 2022

Excerpt from submission:

3. **Revise the statement, (b) (4) to read "Dosage: See prescribing information."**

Response: The vial and carton labels have been revised to read "Dosage: See prescribing information."

1. **Ensure the presentation of the proper name is at least half the size of the proprietary name per CFR 201.10(g)(2).**

Response: Eisai confirms that the proper name on the carton is at least half the size of the proprietary name.

2. **To improve prominence and readability, we recommend increasing the prominence (i.e., font size) of the strength, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6).**

Response: The prominence of the strength has been increased on the updated carton labels.

3. **Clarify what information is contained in the QR code, as well as include the machine-readable (2D data matrix barcode) product identifier information and intended location on the carton labeling. We recommend you review the Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021) available from:** https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Response: If approved, the QR code will link to the approved USPI on the LEQEMBI brand website. Per your request the location of the DSCSA-compliant 2D matrix barcode has been identified on the carton label.

Container labels

(b) (4)

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/s/

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STEPHANIE L DEGRAW
10/07/2022 03:24:51 PM

Clinical Inspection Summary

Date	09/12/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D., (Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Emilios (Andrew) Papanastasiou, M.S., Pharm.D., Regulatory Project Manager Kevin Krudys, Ph.D., Clinical Reviewer Ranjit Mani, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
BLA #	761269
Applicant	Eisai Inc.
Drug	Lecanemab
NME	Yes
Proposed Indication	Treatment of early Alzheimer's disease
Consultation Request Date	2/7/2022
Summary Goal Date	8/2022, extended to 9/16/2022
Priority/Standard Review	Priority
Action Goal Date	1/7/2023
PDUFA Date	1/7/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Goodman, Nardandrea, and Watson were inspected in support of this BLA, covering Protocol BAN2401-G000-201. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Both quantitative and qualitative Positron Emission Tomography (PET) amyloid data were verified with no discrepancies identified. Individual and total scores from the three scales comprising the Alzheimer's Disease Composite Score (ADCOMS), the primary efficacy endpoint, were also verified with no discrepancies identified. Additionally, there was no evidence of underreporting of adverse events.

II. BACKGROUND

Lecanemab injection for intravenous use is being developed under BLA 761269 (IND 105081) for the treatment of early Alzheimer's disease.

The sponsor has submitted a Phase 2 study, Protocol BAN2401-G000-201, to support the efficacy and safety of lecanemab for the treatment of early Alzheimer's disease. The sponsor is seeking approval under the accelerated approval pathway based on the biological endpoint, reduction in amyloid beta plaques. A Phase 3 confirmatory clinical trial is ongoing.

Protocol BAN2401-G000-201

Title: "A placebo-controlled, double-blind, parallel-group, Bayesian adaptive randomization design and dose regimen-finding study with an open-label extension phase to evaluate safety, tolerability and efficacy of BAN2401 in subjects with early Alzheimer's Disease"

Subjects: 856 randomized

Sites: 108 sites in the North America (71 [65 in United States]), Western Europe (19), Asia/Pacific (18)

Study Initiation and Completion Dates: 12/20/2012 – 7/19/2018 (21-month data, Core study)*;* the open-label extension phase of the protocol is ongoing

Interim Data Cut-off Date: 6/30/2021

This was a double-blind, parallel-group, placebo-controlled Phase 2 study that used a dose-finding, response adaptive randomization design to evaluate the safety, tolerability, and efficacy of lecanemab (BAN2401) in subjects with mild cognitive impairment due to Alzheimer's disease (AD) or mild AD dementia.

Eligibility criteria included males or females, 50 to 90 years of age; diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia (see below); objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory subscale II (WMS-IV LMII); positive amyloid load as indicated by PET assessment of imaging agent uptake into brain or CSF assessment of Aβ(1-42); Mini-Mental State Examination (MMSE) score $\geq$22 and $\leq$30; if taking anticholinesterase inhibitors/memantine, dose must be stable for at least 12 weeks prior to baseline; and must have an identified caregiver/informant.

Mild Cognitive Impairment due to Alzheimer's disease – intermediate likelihood was defined as:

1. Subjects who meet the National Institute of Aging-Alzheimer's Association (NIA-AA) core clinical criteria for mild cognitive impairment due to Alzheimer's disease – intermediate likelihood
2. Subjects who have a Clinical Dementia Rating (CDR) score of 0.5 and a CDR-Sum of Boxes (CDR-SB) score $\geq$0.5 at screening and baseline
3. Subjects who report a history of subjective memory decline with gradual onset and slow progression over 1 year before screening and must be corroborated by an

informant

Mild Alzheimer's disease dementia defined as:

1. Subjects who met the NIA-AA core clinical criteria for probable Alzheimer's disease dementia
2. Subjects who have a CDR score of 0.5 to 1.0 and CDR-SB score ≥0.5 at screening and baseline

The study was comprised of 5 phases (screening, baseline, core study, follow-up visit, and open-label extension phase):

Screening (Day -60 to Day -31)
Subjects were screened for study eligibility. Assessments included but were not limited to, labs, clinical assessments, and MRI.

Baseline (Day -30 to Day -1)
Baseline assessments included, but were not limited to, labs, clinical assessments, amyloid PET or cerebrospinal fluid (CSF) Aβ(1-42),and Apolipoprotein E (*APOE*) status.

Core Study (Weeks 1 to 79)
Subjects were initially randomized (4:2:2:2:2:2) to the following study arms with the exception that subjects who were confirmed *APOE* positive were not randomized to the lecanemab 10 mg/kg every two week arm (per Amendment 4, 7/9/2014):

- Placebo
- Lecanemab 2.5 mg infusion every two weeks
- Lecanemab 5 mg infusion every two weeks
- Lecanemab 10 mg infusion every two weeks
- Lecanemab 5 mg infusion every month
- Lecanemab 10 mg infusion every month

After 196 subjects were randomized, an interim analysis was planned and response adaptive randomization (RAR) used to guide subsequent randomization into study arms. Randomization was stratified by *APOE* status (positive or negative) and presence or absence of ongoing AD treatment with anticholinesterase inhibitors, memantine, or both.

Additional PET scans or CSF samples were collected at 12 and 18 months for those subjects consenting to these procedures (per Amendment 8).

Follow-up Visit (Week 90)
For subjects not continuing in the open-label extension phase, a follow-up visit occurred at 3 months after the last dose of IP.

Open-Label Extension Phase (24 months)
This open-label extension phase was added in Amendment 11 (9/14/2018). Subjects completing the 79-week Core phase of the study could continue into the open-label extension phase. All subjects in the open-label extension phase received lecanemab 10 mg/kg biweekly, including *APOE 4* positive subjects.

Per protocol, the *primary efficacy endpoint* was the change from baseline in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months. There were a number of key secondary endpoints which included the change from baseline to 18 months in the following: brain amyloid as measured by amyloid PET, ADCOMS, CDR-SB, ADAS-Cog.

The sponsor is submitting this BLA under the accelerated approval pathway with data for the biological endpoint, change from baseline to 18 months in brain amyloid as measured by PET, to support efficacy.

Rationale for Site Selection

Clinical sites for BIMO inspections were selected based on risk ranking in the clinical investigator site selection tool (CISST), enrollment in lecanemab dose arm for proposed efficacy, numbers of subjects with amyloid PET scan data, and prior inspections.

III. RESULTS

1. Ira Goodman, M.D.
Site #1001
Bioclinica Research Synexus Clinica Research US Inc.
100 W. Gore Street
Orlando, FL 32806
Inspection Dates: 6/21/2022 – 7/5/2022

At this site for Protocol BAN2401-G000-201 (Core), 291 subjects were screened, 67 subjects were randomized, and 42 subjects completed the study. Twenty-five subjects (17 randomized to lecanemab, 8 randomized to placebo) discontinued the study. Reasons for discontinuation were not provided on the screening and enrollment log and, due to time constraints, were not further evaluated during the inspection.

Informed consent forms were reviewed for 129 of 291 (44.3%) subjects screened and included all 69 subjects who were randomized. Signed informed consent forms, dated prior to participation in the study, were present for all subjects reviewed. An audit of the study records for 32 of 69 (46.4%) randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations,

biological efficacy data (Positron Emission Tomography [PET]), and primary efficacy data (Alzheimer's Disease Composite Score [ADCOMS]).

Upon request, and after the inspection was announced, the sponsor obtained certified copies of PET amyloid quantitative data from the vendor, (b) (4). The certified copies were sent to the clinical site and submitted to the BLA. Efficacy verification focused on the 32 subjects with PET data for all three study timepoints: Baseline, Week 53, and Week 79. Data for two PET parameters, Global Cortical Average Standard Uptake Value (SUV) and Region Whole Cerebellum Mask SUV, were verified against sponsor data line listings; no discrepancies were identified.

In addition to the PET quantitative data, PET qualitative data were also verified. Qualitative visual reads for the presence (positive) or absence (negative) of amyloid were conducted by two blinded central readers. If there was a discrepancy between the two readers, the readers met to reach a consensus that was documented on the Visual Interpretation Consensus Form. This reviewer reviewed the qualitative PET readings submitted to the BLA. Disparate readings between the two readers were noted for at least one timepoint in 13 of 67 (19.4%) randomized subjects. Consensus readings of positive and negative were noted in subjects randomized to both lecanemab and placebo arms.

The primary efficacy endpoint was the change in ADCOMS at 12 months. The ADCOMS is a weighted linear combination of 12 items from three clinical scales: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), and Clinical Dementia Rating (CDR). Individual and total scores from these three scales were verified against sponsor data line listings for the 32 subjects with PET data for all three study timepoints; no discrepancies were identified. Additionally, there was no evidence of underreporting of adverse events.

2. John Nardandrea, M.D.
Site #1034
Renstar Medical Research
Ocala, FL 34470
Inspection Dates: 7/13/2022 – 7/19/2022

At this site for Protocol BAN2401-G000-201 (Core), 84 subjects were screened, 40 subjects were randomized, and 31 subjects completed the study. Nine subjects (7 randomized to lecanemab, 2 randomized to placebo) discontinued the study. Reasons for discontinuation were not provided on the screening and enrollment log and, due to time constraints, were not further evaluated during the inspection.

Informed consent forms were reviewed for 28 of 40 (70.0%) randomized subjects. Signed informed consent forms, dated prior to participation in the study, were present for all subjects reviewed. An audit of the study records for 28 of 40 (70.0%) randomized subjects

was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, biological efficacy data (PET amyloid), and primary efficacy data (ADCOMS).

Upon request, and after the inspection was announced, the sponsor obtained certified copies of PET amyloid quantitative data from the vendor, (b) (4). The certified copies were sent to the site and submitted to the BLA. Efficacy verification focused on the 27 subjects with PET data for all three study timepoints: Baseline, Week 53, and Week 79. Data for two PET parameters, Global Cortical Average Standard Uptake Value (SUV) and Region Whole Cerebellum Mask SUV, were verified against sponsor data line listings; no discrepancies were identified.

In addition to the PET quantitative data, PET qualitative data was also verified. This reviewer reviewed the qualitative PET readings submitted to the BLA. Disparate readings between the two readers were noted for one timepoint in 9 of 40 (22.5%) randomized subjects. Consensus readings of positive and negative were noted in subjects randomized to both lecanemab and placebo arms.

The primary efficacy endpoint was the change in ADCOMS at 12 months. The ADCOMS is a weighted linear combination of 12 items from three clinical scales: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), and Clinical Dementia Rating (CDR). Individual and total scores from these three scales were verified against sponsor data line listings for the 32 subjects with PET data for all three study timepoints; no discrepancies were identified. Additionally, there was no evidence of underreporting of adverse events.

Two dosing errors occurred in two of 40 (5%) subjects at this site.

- Subject (b) (6), randomized to lecanemab 10 mg/kg monthly, was dispensed the wrong kit number at Visit 19/Week 33 and received placebo. The error was caught by the infusion nurse approximately ten minutes after the infusion was started. The infusion was stopped after identification of the error; the subject had received 40 ml of placebo. The subject was then administered the correct investigational product (IP). This dosing error was reported to both the sponsor and IRB, and site staff implemented a triple authentication process to review infusion bags prior to IP administration. This dosing error was included in the sponsor's protocol deviation line listing.
- Subject (b) (6), randomized to placebo, was administered the incorrect kit number/IP vial at Visit 28/Week 51 and received lecanemab. The error was discovered one week later and was reported to the sponsor and the IRB. The site

implemented a corrective and preventive action (CAPA) plan to prevent recurrence of this error. This dosing error was not included in the sponsor's protocol deviation line listing but was reflected elsewhere in the submission (Listing 16.1.6 Listing of Subjects by Batch Number).

Reviewer comments: Two dosing errors occurred in two of 40 randomized subjects. The site implemented CAPAs to prevent recurrence of the errors and reported the errors to the sponsor and the IRB. Both errors were limited to a single visit occurring earlier than the Week 79 PET amyloid timepoint of interest for the biological efficacy endpoint. It is unlikely that these two dosing errors would impact the overall efficacy analysis.

3. David Watson, Psy.D.
Site #1090
Alzheimer's Research and Treatment Center
2767 S. State Road 7, Suite 300
Wellington, FL 33414
Inspection Dates: 7/25/2022 – 8/12/2022

At this site for Protocol BAN2401-G000-201 (Core), 247 subjects were screened, 69 subjects were randomized, and 47 subjects completed the study. Twenty-two subjects (18 randomized to lecanemab, 4 randomized to placebo) discontinued the study. Reasons for discontinuation were not provided on the screening and enrollment log and, due to time constraints, were not further evaluated during the inspection.

Informed consent forms were reviewed for 15 of 247 (6.1%) screened subjects. Signed informed consent forms, dated prior to participation in the study, were present for all subjects reviewed. An audit of the study records for 36 of 70 (51.4%) randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, biological efficacy data (PET amyloid), and primary efficacy data (ADCOMS).

Upon request, and after the inspection was announced, the sponsor obtained certified copies of PET amyloid quantitative data from the vendor, (b) (4). The certified copies were sent to the clinical site and submitted to the BLA. Efficacy verification focused on the 36 subjects with PET data for all three study timepoints: Baseline, Week 53, and Week 79. Data for two PET parameters, Global Cortical Average Standard Uptake Value (SUV) and Region Whole Cerebellum Mask SUV, were verified against sponsor data line listings; no discrepancies were identified.

In addition to the PET quantitative data, PET qualitative data was also verified. This reviewer reviewed the qualitative PET readings submitted to the BLA. Disparate readings between the

two readers were noted for one timepoint in 23 of 69 (33.0%) randomized subjects. Consensus readings of positive and negative were noted in subjects randomized to both lecanemab and placebo arms.

The primary efficacy endpoint was the change in ADCOMS at 12 months. The ADCOMS is a weighted linear combination of 12 items from three clinical scales: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), and Clinical Dementia Rating (CDR). Individual and total scores from these three scales were verified against sponsor data line listings for the 32 subjects with PET data for all three study timepoints; no discrepancies were identified. Additionally, there was no evidence of underreporting of adverse events.

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Clinical Analyst
Good Clinical Practice Assessment Branch
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JENN W SELLERS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 19, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761269
Product Name and Strength:	Leqembi (lecanemab-irmb) Injection, 200 mg/2 mL (100 mg/mL) and 500 mg/5 mL (100 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eisai Inc.
FDA Received Date:	December 14, 2021 and April 12, 2022
OSE RCM #:	2022-88
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader (Acting):	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Leqembi (lecanemab-irmb) injection, the Division of Neurology 1 (DN 1) requested that we review the proposed Leqembi prescribing information (PI), medication guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
PROPOSED REVISIONS TO SECTION 2 DOSAGE AND ADMINISTRATION	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), medication guide (MG), container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 (Table 2) for the Division and in Section 5 (Table 3) for Eisai Inc.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The infusion instructions in the 5th bullet point do not include the infusion time.	Incomplete administration instructions may lead to incorrect infusion time during treatment.	To increase clarity, we recommend revising (b) (4) "Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter." We note this recommendation aligns with the Aduhelm (aducanumab-avwa) injection PI.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The package type term (b) (4) is used in Section 2.4 "Dilution Instructions" to describe the package type.	(b) (4) is not a recommended package type term and is inconsistent with the package type term "single dose" that is used in all other sections of the PI as well as on the container and carton labeling.	We recommend revising (b) (4) to read "Each vial of Tradename is intended for single-dose only." Also refer to comment #2 directly below.
2.	The information presented in Section 2 is lacking clarity and contains instances of passive voice.	This section may be improved to provide more detailed instructions for safe use of the drug product and to use more direct language (i.e., active voice).	See Appendix E for recommendations for Section 2 Dosage and Administration for your consideration.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The (b) (4) storage information presented in Section 16 How Supplied/Storage and Handling can be improved for clarity or removed.	Drug storage information after dilution may not need to be included in Section 16 as it is stated in Section 2 Dosage and Administration. However, if included in Section 16, the storage information may be improved to provide more detailed information and to use more direct language (i.e., active voice).	We recommend removing after dilution storage information in Section 16 and replacing it with the following: "For information on stability and storage of diluted TRADENAME, see *Dosage and Administration (2.4)*." Alternatively, see Appendix E for recommendations for the storage statement of diluted TRADENAME for your consideration.

5 RECOMMENDATIONS FOR EISAI INC

Table 3. Identified Issues and Recommendations for Eisai Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The dosage statement can be improved.	To ensure consistency with the physician labeling rule (PLR) formatted Prescribing Information.	Revise the statement, (b) (4) to read "Dosage: See prescribing information."
Carton Labeling			
1.	It is unclear if the established name is at least half the size of the proprietary name.	The established name does not appear to be presented in accordance with 21 CFR 201.10(g)(2).	Ensure the presentation of the established name is at least half the size of the proprietary name per CFR 201.10(g)(2).
2.	The strength statement lacks prominence.	Product strength is critical information and should be prominent on the principal display panel per our F*inal Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors	To improve prominence and readability, we recommend increasing the prominence (i.e., font size) of the strength, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6).
3.	As currently presented, it is unclear if the QR barcode located on the side panel of the carton labeling is intended to represent the product	The Drug Supply Chain Security Act (DSCSA) guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product	Clarify what information is contained in the QR code, as well as include the machine-readable (2D data matrix barcode) product identifier

Table 3. Identified Issues and Recommendations for Eisai Inc (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	identifier information (i.e., on your proposed carton labeling, GTIN, SN, EXP and LOT). If this is intended to be the machine-readable portion of the product identifier, then it is not an acceptable format for this product identifier.	identifier and a human-readable product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]	information and intended location on the carton labeling. We recommend you review the *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (June 2021) available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Leqembi that Eisai Inc submitted on December 14, 2021.

Table 4. Relevant Product Information for Leqembi	
Initial Approval Date	N/A
Active Ingredient	lecanemab
Indication	For the treatment of Early Alzheimer's Disease (mild cognitive impairment due to AD and mild AD dementia, with confirmed amyloid pathology).
Route of Administration	Intravenous
Dosage Form	Injection
Strength	200 mg/2 mL (100 mg/mL) and 500 mg/5 mL (100 mg/mL)
Dose and Frequency	The recommended starting and maintenance dose is 10 mg/kg administered as an intravenous infusion over approximately one hour, once every two weeks
How Supplied	500 mg/5 mL (100 mg/mL) single-dose vial (with white flip cap) 200 mg/2 mL (100 mg/mL) single-dose vial (with dark grey flip cap)
Storage	Store unopened vials of LEQEMBI in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. After dilution, immediate use is recommended. If not administered immediately, LEQEMBI may be stored up to (b) (4) hours at a refrigerated temperature (2°C to 8°C [36°F to 46°F]), or at room temperature up to 30°C (86°F) for up to (b) (4) hours. Do not freeze or shake vials of LEQEMBI.
Container Closure	In a glass vial with an elastomeric closure.

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Leqembi labels and labeling submitted by Eisai Inc. received on April 12, 2022.

- Container labels (clean and annotated)
- Carton labeling (clean and annotated)
- Prescribing Information and Medication Guide (Images not shown) available from docuBridge via

  Clean: \\CDSESUB1\evsprod\bla761269\0027\m1\us\11413-draft-labeling-text.pdf

  Track: \\CDSESUB1\evsprod\bla761269\0027\m1\us\11413-draft-labeling-text-tc.pdf

F.2 Label and Labeling Images

Container labels

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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