September 30, 2021

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

RE: Food and Drug Administration's Label of Biogen's Aducanumab

Dear Dr. Cavazzoni:

The undersigned organizations write to express our concern that the Food and Drug Administration's (FDA) label for the dispensing of aducanumab for patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) differs significantly from what was studied in the Phase III clinical trials. Our societies would welcome the opportunity to engage with the FDA in a discussion of these issues, which we've outlined below, including whether revisions to the FDA label are warranted.

With the recent FDA approval of aducanumab, our joint members and other clinicians are being asked about whether this new treatment is right for their patients. We are each developing preliminary advice to guide our members to ensure that patients and their surrogates are fully informed about the risks and benefits of this new treatment based on available data. Currently, however, there is a clear disconnect between the clinical trial design and the labeling or indications for use of aducanumab (see Table 1 below).

The FDA approved indications for use of aducanumab includes a much wider range of patients than were studied in the Phase III clinical trials. Specifically:

- The revised label (July 8th) fails to clearly note that aducanumab was used for the treatment of generally healthy patients with mild cognitive impairment or mild dementia (confirmed using validated tools) due to Alzheimer's disease with confirmed presence of amyloid plaque, the population in which treatment was initiated in clinical trials.
- The label does not require a PET scan be performed before aducanumab can be prescribed even though all patients in the clinical trials were required to have a positive beta amyloid PET scan.
- The label requires MRIs be performed to identify amyloid-related imaging abnormalities (ARIAs) due to cerebral microhemorrhages and cerebral edema. In the clinical trial, patients with ARIAs had aducanumab use suspended until they resolved but the label contains no such requirement for suspension when ARIAs are identified.

Furthermore, the label does not list any contraindications even though aducanumab was only studied in generally healthy patients. To fully inform people living with Alzheimer's disease and those who love them, the label should include information about who was EXCLUDED from the aducanumab clinical trials since no safety and efficacy data is available for this population.

We understand the heavy toll of Alzheimer's disease on patients, caregivers, and their families and are fully supportive of FDA approving safe and effective new treatments; however, we remain concerned that aducanumab was approved for use in populations that were not included in the clinical trials.

Our societies would be pleased to discuss this letter with you further. Please contact Alanna Goldstein agoldstein@americangeriatrics.org or call 212-308-1414, if you have any questions.

Sincerely,

American Geriatrics Society

AMDA – Society for Post-Acute and Long-Term Care Medicine

Society of General Internal Medicine

Society of Nuclear Medicine and Molecular Imaging

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Table 1: Differences between what FDA Approved and what was Studied

Clinicians should know that the FDA approval of aducanumab differs significantly from what was studied in the trials as highlighted in Table 1 below.

FDA Label	Clinical Trials (ENGAGE, EMERGE)
Population	
Aduhelm™ is indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm™ 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. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.	Aducanumab was only studied in people who had: • A positive amyloid positron emission tomography (PET scan); AND • Mild cognitive impairment or mild dementia due to Alzheimer's disease. A total of 1105 patients received aducanumab 10 mg/kg. 52% were women, 76% were White, 10% were Asian, and 3% were of Hispanic or Latino ethnicity. The mean age at study entry was 70 years (range from 50 to 85). Individuals with dementia stages earlier or later than 'mild' were not studied.
Contraindications and Trial Exclusion Criteria	
The label does not specify contraindications	<u>Patients were excluded from the clinical trial if they met any of the following exclusion criteria:</u> 1. Over the age of 85 2. Any uncontrolled medical condition 3. Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to screening 4. Brain MRI performed at screening that shows evidence of any of the following: acute or sub-acute hemorrhage, prior microhemorrhage or prior subarachnoid hemorrhage (unless finding is not due to an underlying structural or vascular hemorrhage), more than 4 microhemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis, or history of diffuse white matter disease. 5. Contraindications to having a brain MRI or PET scan 6. History of bleeding disorder 7. Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤325 mg daily) 8. Uncontrolled hypertension or history of unstable angina, myocardial infarction, chronic heart failure, or clinically significant conduction abnormalities

Determining level of cognitive impairment and presence of amyloid plaque	
The label does not require any diagnostic tests before this drug is prescribed.	Before enrollment in either of the two trials, patients were required to undergo both an amyloid PET scan and detailed cognitive testing and staging.
Ongoing screening to assess benefit to patients	
None	Patients underwent repeated PET scans and cognitive assessments during the trials.
Screening and treatment protocol for adverse events	
• Obtain baseline MRI within one year prior to initiating treatment. • Obtain MRIs prior to the 7th and 12th infusions. • If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).	• ARIA monitoring methods and data collection throughout the aducanumab clinical program included routine brain MRI scans performed for all participants at protocol-specified timepoints, follow-up MRI scans performed for participants in whom ARIA was detected, and a centralized MRI reader staffed with expert radiologists highly experienced with ARIA. • In the clinical trial, patients with ARIAs had aducanumab use suspended until they resolved. Follow-up brain MRIs for participants who developed ARIA were performed every 4 weeks until ARIA resolved (ARIA-E) or stabilized (ARIA-H).