AAN Comments to CMS on Coverage for Aducanumab

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The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 36,000 neurologists and clinical neuroscience professionals. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a physician with specialized training in diagnosing, treating, and managing disorders of the brain and nervous system. These disorders affect one in six people and include conditions such as multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

The AAN has concerns with the process that resulted in the approval of aducanumab. However, as our members are determining how and when they will utilize aducanumab, the AAN wishes to pass along their perspective as CMS develops this National Coverage Determination (NCD). The statements below are not intended to be in support of the drug or opposition to its use. Rather, we feel it is important to inform the Centers for Medicare and Medicaid Services of our perspective as representatives from the neurology community.

Our responses to the questions raised by the agency are answered below:

1. Which health outcomes are important, and what degree of improvement in them is meaningful for patients receiving treatment?

Stabilization, improvement, or meaningful slowing of decline in cognitive function and independent functioning, both in the community and at home, are the most meaningful outcomes for a patient receiving these treatments. These outcomes can be measured by using standardized dementia scales and other functional measures. Examples of dementia scales the AAN would recommend include MMSE, MOCA, CDR-SB, Katz ADL, and Lawton IADL. Due to varying rates of decline among the patient population, even using objective scales it might be difficult for a patient being treated to tell if their decline is occurring less quickly on therapy. Therefore, insight from the treating physician is necessary.

2. What characteristics of patients with Alzheimer's disease are important to optimizing the likelihood of positive health outcomes from treatment?

The patient criteria used in the clinical trials seem most appropriate for optimizing the likelihood of positive health outcomes. A patient should have a diagnosis of mild Alzheimer's disease or mild cognitive impairment due to Alzheimer's disease (MMSE between 24-30 and CDR of 0.5). Additionally, proof of beta-amyloid pathology is needed and baseline MRI with fewer than 4 microhemorrhages and no evidence of superficial siderosis. Patients with ApoE4 alleles seemed to have both more benefit from the drug as well as more amyloid related imaging abnormalities (ARIA). Contraindications include a primary diagnosis of cerebral amyloid angiopathy or the use of anticoagulation. The clinical trials for aducanumab lacked sufficient diversity in their enrolled populations. This underrepresentation should be addressed in the phase four trial by working to recruit a representative trial population and ensure financial barriers do not prevent participation. Additional characteristics important for

positive outcomes include the patient having a reliable care partner and the patient having reliable transportation to get to monthly infusion appointments.

Eligible patients should be informed by their provider of open studies for this class of drugs, and providers should encourage participation when appropriate. If a patient is does not wish to or is not able to join a trial, but still wishes to begin treatment, then the provider should proceed to offer this class of drugs outside of the trial.

3. What issues of equity and inclusion must be accounted for in the diagnosis and treatment of Alzheimer's disease?

In general, access to imaging, CSF analysis, infusion facilities, and a care team comfortable with diagnosis and treatment with this drug may pose challenges to those outside of urban areas. In addition, we would encourage regulatory bodies to obtain more data on the use of these drugs in non-white research participants. There are wide disparities in dementia diagnosis and care in Black, Hispanic and Indigenous patients, and low-SES patients. These patients are at elevated risk for dementia yet also encounter delays in diagnosis and other barriers to care. The absence of safety/efficacy data on this class of drugs in these populations is of greatest need and is an unfortunate reflection of these ongoing disparities. Another barrier to care in these underserved communities is the stigma surrounding diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.

4. What health care providers should be included as part of the patient's treatment team? Should medical specialists be included in the care team of patients receiving treatment? If so, which specialists should be included in the care?

Given the complexity and novelty of the therapy, specialty expertise will be an important component of the initiation and management of this treatment. Neurologists, geriatricians, and geriatric psychiatrists specializing in this patient population should be involved in the principal care of a patient that is interested in receiving this class of drugs. Others involved in the patient care team while receiving this medication would be infusion support and radiologists with training and expertise in diagnosing ARIA as well as MRI protocols that detect microhemorrhages.

5. In what setting(s) should treatment and care be given?

The first year of treatment is the highest risk for the development of ARIA, so infusions should be provided in an infusion center during this period. After the first year of infusions, we would support the use in a home infusion setting as eligible patients may have transportation challenges and could benefit from the ability to receive home infusion therapy. While a patient is receiving care at home, they should continue to receive care and be monitored by a member of the care team who has received training in monitoring and caring for patients receiving this class of drug.

Care should be given by a physician who can identify appropriate patient populations to receive this medication (including coordination of screening studies including baseline MRIs and detection of beta-amyloid and completing appropriate cognitive screening) as well as coordinate ongoing management of the patient as they receive therapy (monitoring for clinical and radiographic signs of ARIA) and general monitoring of patient's health and wellbeing.