Kristin Busse, PharmD, BCPS; Abir T. El-Alfy, PhD, MS

Aducanumab

Aducanumab was approved on June 7, 2021 by the US Food and Drug Administration (FDA) using the **accelerated approval pathway**. Under this approval category, a drug must be used for a serious condition that fills an unmet medical need. The outcomes in the study are based on surrogate endpoints thought to predict clinical benefit but are not themselves a measure of clinical benefit.

First-of-its-kind treatment approved for Alzheimer's disease

INDICATION

Treatment of patients with mild cognitive impairment or mild dementia stage of Alzheimer's disease.

MECHANISM OF ACTION

Human immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta.

REGULATORY CONTROVERSIES

The Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee reviewed the application in November 2020 and voted (10 members against and 1 member uncertain) that it was unreasonable to consider the evidence of clinical benefit from Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease. This vote was largely based on conflicting results of Study 302 and Study 301.

COST

Current cost is $56,000 annually. To be considered cost-effective, the drug should be reduced to $1200-$4200 annually, according to Institute for Clinical and Economic Review (ICER).

• • •

Author Affiliations: Medical College of Wisconsin School of Pharmacy, Milwaukee, Wis (Busse, El-Alfy); email wmj@med.wisc.edu.

Financial Disclosures: None declared.

References: Available upon request.

EMERGE AND ENGAGE CLINICAL TRIAL RESULTS

Design: Placebo controlled, 18-month duration

Surrogate endpoints: Reduction of amyloid beta plaque in the brain

ENGAGE (Study 301, n=1653): No benefit both low and high doses -> Further statistical subgroup analysis indicated a benefit at high dose

EMERGE (Study 302, n=1643): Positive benefit in high-dose group (10 mg/kg). Patients receiving treatment had significant dose-and-time dependent reduction of amyloid beta plaque compared to placebo.

Adverse Effects

At least 10% and higher reported:

- Headache, fall
- Amyloid-related imaging abnormalities (ARIA)
  - Commonly presents as temporary swelling in areas of the brain (found on MRI) that usually resolves over time and does not cause symptoms. Some patients report headache, confusion, dizziness, vision changes or nausea.
  - Observed in 41% of patients treated with aducanumab with planned doses of 10 mg/kg vs 10% of patients on placebo. Recently, concerns were raised after a trial participant receiving the drug died with evidence of brain swelling.

CONCLUSION

The FDA required the drug company to conduct a new randomized, controlled trial to verify the drug's clinical benefit.

Published online April 2, 2022.