NEW DRUG APPROVAL

Brand Name	Aduhelm™
Generic Name	aducanumab-avwa, injection
Drug Manufacturer	Biogen Inc

New Drug Approval

FDA Approval Date: June 7, 2021
Review Designation: N/A
Type of Review: Biologic License Application (BLA): 761178
Dispensing Restrictions: Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Alzheimer disease (AD) is a neurodegenerative disorder of uncertain cause and pathogenesis that primarily affects older adults and is the most common cause of dementia. The most essential and often earliest clinical manifestation of AD is selective memory impairment, although there are exceptions. While treatments are available that can ameliorate some symptoms of the illness, there is no cure currently available, and the disease inevitably progresses in all patients.
Alzheimer disease (AD) is the most common cause of dementia and one of the leading sources of morbidity and mortality in the aging population.
The hallmark neuropathologic changes of AD are diffuse and neuritic plaques, marked by extracellular amyloid beta deposition, and neurofibrillary tangles, comprised of the intracellular accumulation of hyperphosphorylated tau (p-tau) protein. The epidemiologic study of AD is being transformed by the availability of new biomarker technologies to measure such neuropathologic changes in vivo. Large randomized clinical trials are evaluating anti-amyloid and other disease-based therapies for the treatment and prevention of AD utilizing these imaging or cerebrospinal fluid (CSF) biomarkers.

An estimated 6.2 million Americans suffer from Alzheimer's dementia. Of the total U.S. population, more than 1 in 9 people (11.3%) 65 years of age and older have Alzheimer's dementia; this is projected to reach 12.7 million by 2050. About 5 million Americans 65 years of age and older have mild cognitive impairment (MCI) due to Alzheimer's disease, and roughly 9 million Americans are estimated to have Alzheimer's disease.

Efficacy

Aduhelm™ 's approved indication, "for the treatment of Alzheimer's disease," is the broadest label the FDA could have provided. Clinical trials for the drug were conducted on much more specific patient types: those with mild cognitive impairment (MCI) or mild Alzheimer's dementia.

All patients in the trials also received a positron emission tomography (PET) scan to confirm elevated brain amyloid levels. This diagnostic procedure is not required in the FDA label for Aduhelm™, nor is it generally paid for by Medicare.

Table 1. Cognitive Tests Used to Measure Alzheimer's Disease/Dementia Progression

Test Name	Description	Measures	Notes
MMSE	Includes norms for age, ethnicity, and education; takes 5-8 minutes to administer	Orientation, registration (immediate memory), short-term memory (but not long-term memory), language functioning, limited executive function	**Score** — **Level of Dementia** 24 and higher — Normal cognition; no dementia 19–23 — Mild dementia 10–18 — Moderate dementia 9 and lower — Severe dementia An MMSE score ≥24 for initial approval An MMSE score of <19 indicates moderate to severe dementia for potential discontinuation
RBANS*	A brief, individually administered test that consists of 12 subtests, which yield 5 index scores and a total scale score	Attention, language, visuospatial/constructional abilities, and immediate and delayed memory	**Index Score** — **Classification** 130 and above — Very superior 120–129 — Superior 110–119 — High average 90–109 — Average 80–89 — Low average 70–79 — Borderline 69 and below — Extremely low RBANS ≤85 for initial approval
CDR-GS	A 5-point scale for cognitive impairment	Stages of dementia	**Score** — **Cognitive Impairment** 0 — Normal 0.5 — Very mild dementia 1 — Mild dementia 2 — Moderate dementia 3 — Severe dementia
CDR-GS (cont.)			0 connotes no cognitive impairment; the remaining 4 points are for various stages of dementia. CDR-G = 0.5 for initial approval
CDR-SB	A more detailed quantitative general index than the CDRGS; assesses dementia severity by staging	Cognitive, functional, and social domains are included in overall staging	**Score** — **Dementia Severity** 0 — Normal cognitive functioning 0.5–4.0 — Questionable cognitive impairment 0.5–2.5 — Questionable impairment 3.0–4.0 — Very mild dementia 4.5–9.0 — Mild dementia 9.5–15.5 — Moderate dementia 16.0–18.0 — Severe dementia

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Test Name	**Description**	**Measures**	**Notes**
			A score of >9 indicates moderate to severe dementia for potential discontinuation. CDR-SB scores distinguished MCI from dementia in patients with reasonable accuracy when CDR-GS was restricted to 0.5. The Washington University CDR scale is frequently used to stage dementia severity and yields both a global (CDR-GS) and sum of boxes (CDR-SB) score. CDR-SB score is a more detailed quantitative general index than the CDR-GS and it provides more information than the CDR total score in cases of mild dementia.
ADAS-Cog 13	Considered a gold standard for assessing the efficacy of antidementia treatments	Assesses multiple cognitive domains including memory, language, praxis, and orientation	ADAS-Cog-13 scores range from 0 to 85. Higher scores indicated greater severity. This measure includes all ADAS-Cog-11 items as well as a test of delayed word recall and a number cancellation or maze tasks.
ADCS-ADL-MCI	Cognitive score specific to MCI patients	Change from baseline in ADCS-ADL-MCI score	Evaluation scale completed by caregiver to describe an MCI patient's performance in several activities of daily living.

Abbreviations: ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version); CDR-G, Clinical Dementia Rating - Global Score; CDR-SB, Clinical Dementia Rating Scale – Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini Mental State Exam; RBANS, Repeatable Battery for Assessment of Neuropsychological Status.

Safety

ADVERSE EVENTS

Most common adverse reactions (at least 10% and higher incidence compared to placebo): ARIA-Edema, headache, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and fall.

WARNINGS & PRECAUTIONS

Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with Aduhelm™, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated.

Hypersensitivity Reactions: Angioedema and urticaria have occurred. If a hypersensitivity reaction occurs, promptly discontinue the infusion of Aduhelm™ and initiate appropriate therapy.

CONTRAINDICATIONS

None.

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Clinical Pharmacology

MECHANISMS OF ACTION

Aducanumab-avwa is a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease.

Dose & Administration

ADULTS

After an initial titration schedule, the maintenance dosage of aducanumab is 10 mg/kg IV infusion over 60 minutes given every 4 weeks (at least 21 days apart).

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refers to adult dosing.

RENAL IMPAIRMENT

No studies have been conducted in these patients; however, aducanumab is not expected to undergo renal elimination.

HEPATIC IMPAIRMENT

No studies have been conducted in these patients; however, aducanumab is not expected to undergo metabolism by hepatic enzymes.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection:

- 170 mg/1.7 mL (100 mg/mL) solution in a single-dose vial
- 300 mg/3 mL (100 mg/mL) solution in a single-dose vial