Aduhelm® (aducanumab-avwa)

100 mg/mL injection, for intravenous use

Not actual size.

MANUFACTURER: Biogen

PRODUCT TRADE NAME: ADUHELM

GENERIC NAME: aducanumab-avwa

INDICATION

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. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including ADUHELM, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications.

ApoE ε4 Homozygotes

Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including ADUHELM, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with ADUHELM; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

Consider the benefit of ADUHELM for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with ADUHELM.

Please see additional Important Safety Information throughout and full Prescribing Information, including Boxed Warning.

PRODUCT INFORMATION

How supplied[1]	ADUHELM injection is a preservative-free, sterile, clear to opalescent, and colorless to yellow solution
Storage requirements[1]	Store ADUHELM in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake. If no refrigeration is available, ADUHELM may be stored unopened in its original carton, protected from light, at or below 25°C (77°F) for up to 3 days. Prior to dilution, unopened vials of ADUHELM can be removed from and returned to the refrigerator if necessary. Total combined time out of refrigeration and exposure to light should not exceed 24 hours at room temperature. After dilution, immediate use is recommended. If not administered immediately, store the prepared solution of ADUHELM in 0.9% sodium chloride injection, USP for up to 3 days at 2°C to 8°C (36°F-46°F), or at room temperature up to 30°C (86°F) for up to 12 hours. Do not freeze
Packaging[1]	Single-dose vial
Individual carton information	Dimensions (inches): 2.4769 w x 3.2396 h x 2.3195 d Weight: 0.09 lbs Volume: 18.612051 mL
Shipping case information (36 units per case)	Dimensions (inches): 7.9375 w x 7.25 h x 14.6255 d Weight: 3.7 lbs Volume: 841.65182 mL

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Amyloid Related Imaging Abnormalities

- Monoclonal antibodies directed against aggregated forms of beta amyloid, including ADUHELM, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together
- ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with ADUHELM
- Consider the benefit of ADUHELM for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with ADUHELM

Incidence of ARIA

- Symptomatic ARIA occurred in 10% (110/1105) of patients treated with ADUHELM in Studies 1 and 2. Serious symptoms associated with ARIA were reported in 0.3% of patients treated with ADUHELM. Clinical symptoms associated with ARIA resolved in 88% of patients during the period of observation. Overall, recurrent episodes of ARIA-E were less frequently symptomatic (12%) compared with initial episodes of ARIA-E (25%)

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PRODUCT INFORMATION (cont'd)

WAC[2]	$479.40 per 170 mg/1.7 mL (100 mg/mL) single-dose vial $846.00 per 300 mg/3 mL (100 mg/mL) single-dose vial	
NDC numbers[1]	**NDC 64406-101-01**	170 mg/1.7 mL (100 mg/mL) single-dose vial
	NDC 64406-102-02	300 mg/3 mL (100 mg/mL) single-dose vial
HCPCS code[3]	**J-code**	**J0172:** Injection, aducanumab-avwa, 2 mg
Potential ICD-10-CM codes for Alzheimer's disease diagnosis[4,5]	**G30.0:** Alzheimer's disease with early onset	
	G30.1: Alzheimer's disease with late onset	
	G30.8: Other Alzheimer's disease	
	G31.84: Mild cognitive impairment, so stated	

HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=*International Classification of Diseases, Tenth Revision, Clinical Modification*; NDC=National Drug Code; WAC=wholesale acquisition cost.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Amyloid Related Imaging Abnormalities (cont'd)

Incidence of ARIA (cont'd)

- Including asymptomatic radiographic events, ARIA was observed in 41% (454/1105) of patients treated with ADUHELM 10 mg/kg compared to 10% (111/1087) of patients on placebo in Studies 1 and 2. ARIA-E was observed in 35% (387/1105) of patients treated with ADUHELM 10 mg/kg compared with 3% (29/1087) of patients on placebo. ARIA-H was observed in 28% (312/1105) of patients treated with ADUHELM compared to 9% (94/1087) of patients on placebo. There was no increase in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for ADUHELM compared to placebo
- The overall incidence of seizure, independent of ARIA, was 0.5% in the 10 mg/kg ADUHELM group and 0.8% in the placebo group in Studies 1 and 2. In patients with ARIA in the 10 mg/kg ADUHELM group, the incidence of seizure was 0.7%. Status epilepticus was reported in the placebo-controlled and long-term extension studies in patients treated with ADUHELM

ApoE ε4 Carrier Status and Risk of ARIA

- Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygotes. In Studies 1 and 2, among patients with a known apolipoprotein E ε4 (ApoE ε4) genotype, 17% (182/1103) of patients in the ADUHELM group were ApoE ε4 homozygotes, 51% (564/1103) were heterozygotes, and 32% (357/1103) were noncarriers. The incidence of symptomatic ARIA was higher in ApoE ε4 homozygotes (16%) than in heterozygotes (11%) and noncarriers (5%) among patients treated with ADUHELM. However, the incidence of serious adverse reactions with ARIA-E, including risk of death, persistent or significant disability or incapacity, hospitalization, or other medically important event that may require intervention to prevent serious outcomes, was similar for ApoE ε4 carriers and noncarriers (2% in homozygotes, 1% in heterozygotes, 2% in noncarriers)
- The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with ADUHELM; however, it cannot be determined if they are ApoE ε4 homozygotes and at a higher risk for ARIA. An FDA-authorized test for detection of ApoE ε4 alleles to identify patients at risk of ARIA if treated with ADUHELM is not currently available. Currently available tests used to identify ApoE ε4 alleles may vary in accuracy and design

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PRODUCT INFORMATION (cont'd)

CPT® codes for administration[6]	**Injection and intravenous infusion chemotherapy and other highly complex drug or highly complex biologic agent administration** **96413:** Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
	Therapeutic, prophylactic, and diagnostic injections and infusions (excludes chemotherapy and other highly complex drug or highly complex biologic agent administration) **96365:** Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

CPT=*Current Procedural Terminology*.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Amyloid Related Imaging Abnormalities (cont'd)

Radiographic Findings

- The radiographic severity of ARIA associated with ADUHELM was classified by radiographic criteria. **Mild ARIA-E:** FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm. **Moderate ARIA-E:** FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm. **Severe ARIA-E:** FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted. **Mild ARIA-H microhemorrhage:** ≤ 4 new incident microhemorrhages. **Moderate ARIA-H microhemorrhage**: 5 to 9 new incident microhemorrhages. **Severe ARIA-H microhemorrhage:** 10 or more new incident microhemorrhages. **Mild ARIA-H superficial siderosis:** 1 focal area of superficial siderosis. **Moderate ARIA-H superficial siderosis:** 2 focal areas of superficial siderosis. **Severe ARIA-H superficial siderosis:** > 2 focal areas of superficial siderosis
- The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients treated with ADUHELM was mild in 10% (115/1105) of patients, moderate in 20% (223/1105) of patients, and severe in 4% (49/1105) of patients. Resolution on MRI occurred in 68% of ARIA-E patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with ADUHELM was mild in 14% (154/1105) of patients, moderate in 3% (29/1105) of patients, and severe in 3% (29/1105) patients. The maximum radiographic severity of ARIA-H superficial siderosis in patients treated with ADUHELM was mild in 7% (79/1105) of patients, moderate in 4% (47/1105) of patients, and severe in 3% (36/1105) of patients. Among patients treated with ADUHELM, the incidence of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 11% (20/182), compared to heterozygotes 4% (21/564) or noncarriers 2% (8/357). Among patients treated with ADUHELM, the incidence of severe radiographic ARIA-H (microhemorrhage or superficial siderosis) was highest in ApoE ε4 homozygotes 20% (36/182), compared to heterozygotes 4% (21/564) or noncarriers 2% (6/357)

Intracerebral Hemorrhage

- Intracerebral hemorrhage greater than 1 cm in diameter was reported in 0.5% (6/1105) of patients in Studies 1 and 2 after treatment with ADUHELM compared to 0.4% (4/1087) of patients on placebo. Fatal events of intracerebral hemorrhage in patients taking ADUHELM have been observed

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Amyloid Related Imaging Abnormalities (cont'd)

Concomitant Antithrombotic Medication

- Patients who received ADUHELM and an antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) did not have an increased risk of ARIA-H or intracerebral hemorrhage compared to patients who received placebo and an antithrombotic medication. The majority of exposures to antithrombotic medications were to aspirin; few patients were exposed to other antiplatelet drugs or anticoagulants, limiting any meaningful conclusions about the risk of ARIA or intracerebral hemorrhage in patients taking other antiplatelet drugs or anticoagulants
- Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking ADUHELM, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with ADUHELM

Other Risk Factors for Intracerebral Hemorrhage

- Patients were excluded from enrollment in Studies 1 and 2 for findings on neuroimaging that indicated an increased risk for intracerebral hemorrhage. These included findings suggestive of cerebral amyloid angiopathy (prior intracerebral hemorrhage greater than 1 cm in diameter, more than 4 microhemorrhages, superficial siderosis, and history of diffuse white matter disease). Vasogenic edema could also be suggestive of cerebral amyloid angiopathy. These and other lesions (aneurysm, vascular malformation) could potentially increase the risk of intracerebral hemorrhage.
- The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy which has an increased risk for intracerebral hemorrhage
- Caution should be exercised when considering the use of ADUHELM in patients with factors that indicate an increased risk for intracerebral hemorrhage and in particular for patients who need to be on anticoagulant therapy

Monitoring and Dose Management Guidelines

- Recommendations for dosing in patients with ARIA-E depend on clinical symptoms and radiographic severity. Recommendations for dosing in patients with ARIA-H depend on the type of ARIA-H and radiographic severity. Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E
- Baseline brain MRI and periodic monitoring with MRI are recommended. Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with ADUHELM, particularly during titration. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment
- There is limited experience in patients who continued dosing through symptomatic ARIA-E or through asymptomatic moderate or severe ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E

Hypersensitivity Reactions

- Angioedema and urticaria were reported in one patient in the placebo-controlled period of Studies 1 and 2, and occurred during the ADUHELM infusion. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy

ADVERSE REACTIONS

- In the combined placebo-controlled and long-term extension periods, 5% (66 out of 1386) of patients in the 10 mg/kg dose group withdrew from the study because of an adverse reaction. The most common adverse reaction resulting in study withdrawal in the combined placebo-controlled and long-term extension periods was ARIA-H superficial siderosis
- The most common adverse reactions reported in at least 2% of patients treated with ADUHELM 10 mg/kg and at least 2% more frequently than in patients on placebo in Studies 1 and 2 were ARIA-E, headache, ARIA-H microhemorrhage, ARIA-H superficial siderosis, fall, diarrhea, and confusion/delirium/altered mental status/disorientation

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References: 1. ADUHELM [Prescribing Information]. Cambridge, MA: Biogen; February 2023. **2.** Biogen. Data on file. **3.** HCPCS code J0172. HCPCS Codes website. https://hcpcs.codes/j-codes/J0172/. Accessed February 16, 2023. **4.** Alzheimer's disease G30. ICD10Data website. https://www.icd10data.com/ICD10CM/Codes/G00-G99/G30-G32/G30-. Accessed February 16, 2023. **5.** Alzheimer's disease G31. ICD10Data website. https://www.icd10data.com/ICD10CM/Codes/G00-G99/G30-G32/G31-. Accessed February 16, 2023. **6.** American Medical Association. *CPT® 2020 Professional Edition.* Chicago, IL: American Medical Association; 2019.

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ADU-US-0613v7 12/23

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