

New Drug Overview

Leqembi and Leqembi Iqlik (lecanemab-irmb)

PDL Category: Central Nervous System Agents

Introduction

Disease Background:

- Unless otherwise noted or in certain portions of the review, the term Leqembi may include both the intravenous (IV) formulation and the subcutaneous (SC) formulation. The SC formulation is known as Leqembi Iqlik.
- Alzheimer's dementia is a neurodegenerative disease described as a slow development of cognitive and memory impairment. It generally involves older adults who are 65 years of age or older and it impedes daily activities and function (*Bennett et al 2025, Wolk and Dickerson 2024*).
 - Late-onset Alzheimer disease (AD) is generally referred to as AD that starts in the elderly (>65 years of age). It is estimated that at least 96% of cases are late-onset AD (*Bennett et al 2025*).
 - Early onset dementia (EOD) generally affects cognition and behavior in adults between the ages of 45 and 65 years of age.
 - It is estimated that about 7.1 million Americans currently have AD symptoms (*NIH 2025*).
- Risk factors for AD that are considered modifiable comprises cardiovascular risk factors, late-life depression, and midlife hearing loss (*Bennett et al 2025*).
- The pathogenesis of AD includes both neurofibrillary tangles (encompassing tau protein) and plaques of beta-amyloid proteins (*Bennett et al 2025*).
 - These biomarkers are now being studied to assist in diagnosis of adults with suspected AD.
- The main symptoms of AD are memory impairment, executive function and judgement issues, and behavioral symptoms. Other signs and symptoms may include apraxia, olfactory dysfunction, disturbance with sleep, seizures (happens in approximately 10-20% of AD patients, generally in the later stages), or motor signs (*Wolk and Dickerson 2024*).
- Oral and transdermal treatment, including cholinesterase inhibitors and memantine, are available to help slow progression of the disease. They are generally offered for mild to moderate AD. In addition, for patients with mild Alzheimer's dementia or mild cognitive impairment, monoclonal antibody disease-modifying treatments are FDA approved. These agents target beta-amyloid (*Bennett et al 2025*).
- Leqembi (lecanemab-irmb) for intravenous infusion was FDA approved in 2023. Leqembi Iqlik for subcutaneous administration was FDA approved in 2025.

Pharmacology/Usage

- Leqembi (lecanemab-irmb) is a recombinant humanized 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.
 - Leqembi reduces amyloid beta plaques, as assessed in Study 1 and Study 2.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Leqembi (lecanemab-irmb)
<ul style="list-style-type: none"> • For the treatment of Alzheimer's disease. Treatment with Leqembi 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. 	✓

(Prescribing information: Leqembi 2026)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Leqembi (lecanemab)	<ul style="list-style-type: none"> • Intravenous (IV) infusion (Leqembi) • Subcutaneous (SC) injection in a single-dose prefilled autoinjector (Leqembi Iqlik) 	IV/SC	<ul style="list-style-type: none"> • Start as an IV infusion using the starting dosage (refer to PI). After 18 months, the starting dosage may be continued or a transition to maintenance dosage regimen may be considered, which can be administered by either IV infusion or SC injection. <ul style="list-style-type: none"> ◦ If transitioning from starting dosage to a maintenance dosage regimen, administer the first maintenance dose two weeks after the last starting dose. • Starting dosage is IV only once every 2 weeks. • Maintenance dosage is IV (Leqembi) once every 4 weeks OR SC (Leqembi Iqlik) once every week. 	<ul style="list-style-type: none"> • Confirm the presence of amyloid beta pathology prior to starting treatment. • During the maintenance dosage regimen, may switch the route of administration. • Leqembi can cause amyloid related imaging abnormalities-edema (ARIA-E) and - hemosiderin (ARIA-H). Obtain a recent baseline brain MRI prior to starting treatment and prior to the 3rd, 5th, 7th, and 14th infusions. • Before injection, remove Leqembi Iqlik from the refrigerator and leave at room temperature for 20 minutes. Do not use an external heat source to heat as heat may damage the product. • Sites for SC injection include the abdomen, upper thigh, and back of the upper arm. Patients and/or caregivers should be instructed on proper SC use.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Leqembi was assessed in two double-blind, placebo-controlled, parallel-group, randomized studies (Study 1 and Study 2) that included patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients in Study 1 and 62% of patients in Study 2] or mild dementia stage of disease [36% of patients in Study 1 and 38% of patients in Study 2], consistent with Stage 3 and Stage 4 Alzheimer's disease).
 - In both studies, patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of ≥ 0.5 .
 - All patients had a Mini-Mental State Examination (MMSE) score of ≥ 22 and ≤ 30 , and had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale; WMS-IV LMII).
 - Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and memantine) for Alzheimer's disease.
 - The dosage of 10mg/kg given once every 2 weeks by IV infusion was assessed in the 18-month placebo-controlled portions of Study 1 and Study 2 and continued in the optional long-term extension in each study.
 - Transitioning to IV 10mg/kg once every 4 weeks or SC 360mg every week after 18 months of dosing is supported by pharmacokinetic and pharmacodynamic modeling using observed data. However, there are limited data to assess the long-term clinical benefit of transitioning to the dosing regimen of IV 10mg/kg once every 4 weeks or SC 360mg every week.
- In Study 1, patients (N=856) were randomized to receive one of 5 doses of IV Leqembi infusion or placebo.
 - Of the total number of patients randomized, 71.4% were ApoE $\epsilon 4$ carriers and 28.6% were ApoE $\epsilon 4$ non-carriers.
 - During the study, the protocol was amended to no longer randomize ApoE $\epsilon 4$ carriers to the 10mg/kg every 2 weeks dose arm. ApoE $\epsilon 4$ carriers who had been receiving Leqembi 10mg/kg every 2 weeks for 6 months or less were discontinued from study drug. As a result, in the Leqembi 10mg/kg every 2 weeks arm, 30.3% of patients were ApoE $\epsilon 4$ carriers and 69.7% were ApoE $\epsilon 4$ non-carriers.
 - At baseline, the mean age of randomized patients was 71 years, with a range of 50 to 90 years. In addition, 50% were male and 90% were white.
- In Study 1, a subgroup of 315 patients were enrolled in the amyloid PET sub study; of these, 277 were assessed at week 79. Results from the amyloid beta PET sub study are presented in the table below, which was adapted from the prescribing information. (Note that p-values were not statistically controlled for multiple comparisons.)

Table 3. Efficacy results

Biomarker Endpoints	Leqembi 10mg/kg Q2 weeks	Placebo
Amyloid Beta PET Composite SUVR	N=44	N=98
Mean baseline	1.373	1.402
Adjusted mean change from baseline at week 79	-0.306	0.004
Difference from placebo; p-value	-0.310; p<0.001	
Amyloid Beta PET Centiloid	N=44	N=98

Biomarker Endpoints	Leqembi 10mg/kg Q2 weeks	Placebo
Mean baseline	78.0	84.8
Adjusted mean change from baseline at week 79	-72.5	1.0
Difference from placebo; p-value	-73.5; p<0.001	

- The primary endpoint was the change from baseline on a weighted composite score consisting of selected items from the Clinical Dementia Rating scale Sum of Boxes (CDR-SB), MMSE, and Alzheimer Disease Assessment Scale- Cognitive Subscale 14 (ADAS-Cog14) at week 53.
 - Results suggested that Leqembi had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at week 53, which did not meet the prespecified success criterion of 80%.
- Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at week 79.
 - Results for clinical assessments demonstrated less change from baseline in CDR-SB and ADAS-Cog14 scores at week 79 in the Leqembi group than in the placebo group (CDR-SB: -0.40; ADAS-Cog14: -2.31).
- After the 79-week double-blind, placebo-controlled period of Study 1, patients could enroll in an open-label extension period for up to 260 weeks, which was initiated after a gap period (range 9 to 59 months; mean 24 months) off treatment.
- *In Study 2*, patients (N=1,795) were randomized to receive IV infusion of Leqembi 10mg/kg or placebo once every 2 weeks. Of the total number of patients randomized, 69% were ApoE ε4 carriers and 31% were ApoE ε4 non-carriers.
 - The median age of patients enrolled was 72 years, with a range of 50 to 90 years. In addition, 52% were women and 77% were White.
 - The randomization was stratified per clinical subgroup (mild cognitive impairment or mild dementia stage of the disease); the presence or absence of concomitant approved therapies for Alzheimer’s disease at baseline (cholinesterase inhibitors and memantine); ApoE ε4 carrier status; and geographical region.
- The primary efficacy outcome was change from baseline at 18 months in the CDR-SB. Key secondary endpoints included change from baseline at 18 months for the following measures: amyloid Positron Emission Tomography (PET) using Centiloids, ADAS-Cog14, and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).
 - Results suggested that Leqembi treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared to placebo at 18 months (-0.45, p<0.0001).
 - Statistically significant differences (p<0.01) between treatment groups were also seen in the results for ADAS-Cog14 and ADCS MCI-ADL at 18 months.
 - Both ApoE ε4 carriers and ApoE ε4 noncarriers demonstrated statistically significant treatment differences for the primary endpoint and all secondary endpoints.
 - In an exploratory subgroup analysis of ApoE ε4 homozygotes, which represented 15% of the trial population, a treatment effect was not observed with Leqembi treatment on the primary endpoint, CDR-SB, compared to placebo, although treatment effects that favored Leqembi were observed for the secondary clinical endpoints, ADAS-Cog14 and ADCS MCI-ADL. Treatment effects on disease-relevant biomarkers (amyloid beta PET, plasma Aβ42/40 ratio, plasma p-tau 181) also favored Leqembi in the ApoE ε4 homozygous subgroup.
 - Starting at 6 months, across all time points, Leqembi treatment demonstrated statistically significant changes in the primary and all key secondary endpoints from baseline compared to placebo.

○ Results are presented in the table below, which was adapted from the prescribing information.

Table 4. Efficacy results

	Leqembi 10mg/kg Q2 weeks	Placebo
CDR-SB	N=859	N=875
Mean baseline	3.17	3.22
Adjusted mean change from baseline at 18 months	1.21	1.66
Difference from placebo, p-value	-0.45, p<0.0001	
ADAS-Cog14	N=854	N=872
Mean baseline	24.45	24.37
Adjusted mean change from baseline at 18 months	4.14	5.58
Difference from placebo, p-value	-1.44, p=0.0007	
ADCS MCI-ADL	N=783	N=796
Mean baseline	41.2	40.9
Adjusted mean change from baseline at 18 months	-3.5	-5.5
Difference from placebo, p-value	2.0, p<0.0001	

- Using population pharmacokinetic modeling and simulation, the intravenous (10mg/kg once every 4 weeks) and subcutaneous (360mg once weekly) maintenance dosing regimens of lecanemab-irmb were predicted to have similar pharmacokinetic exposure.

Clinical guidelines

- There are currently no published guidelines addressing the use of Leqembi.
- There are currently no specific U.S. treatment guidelines found; however, a study called The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management was reviewed (*Atri 2019*).
 - Management includes:
 - First-line options that should be used include nonpharmacologic interventions and behavioral strategies.
 - Eliminate treatments with harmful effects, such as diphenhydramine, other sedative hypnotics, benzodiazepines, or urinary anticholinergic agents.
 - Use antipsychotics with extreme caution.
 - Oral FDA approved medications for AD were listed, including cholinesterase inhibitors and memantine. Not one cholinesterase inhibitor was listed as more effective over another. Combination therapy with a cholinesterase inhibitor and memantine is also discussed.

Safety summary

• Contraindications:

- In patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of Leqembi or Leqembi Iqlik.

• Box Warning:

- Leqembi has a box warning regarding amyloid related imaging abnormalities.
 - Monoclonal antibodies directed against aggregated forms of beta amyloid, including Leqembi, can cause 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, but serious and life-threatening events can occur. ARIA can be fatal. Serious intracerebral hemorrhages >1cm, some of which have been fatal, have been observed in patients treated with this class of medications. As ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy to a patient being treated with Leqembi.
 - ApoE ε4 Homozygotes
 - Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (about 15% of Alzheimer's disease patients) treated with this class of medications, including Leqembi, 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 the start 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 Leqembi; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.
 - Consider the benefit of Leqembi for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to start treatment with Leqembi.

• Warnings and precautions:

- Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with Leqembi. If Leqembi is being administered IV, promptly discontinue the infusion with the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and start appropriate therapy. Leqembi is contraindicated in patients with a history of serious hypersensitivity to lecanemab-irmb or to any excipients of Leqembi or Leqembi Iqlik.
- In Study 2, infusion-related reactions were observed in 26% of patients treated with Leqembi as compared with 7% of patients on placebo. Infusion-related reactions were mostly mild (69%) or moderate (28%) in severity.
 - After the first infusion in Study 1, 38% of patients treated with Leqembi had transient decreased lymphocyte counts to less than $0.9 \times 10^9/L$ compared to 2% in patients on placebo, and 22% of patients treated with Leqembi had transient increased neutrophil counts to greater than $7.9 \times 10^9/L$, compared to 1% of patients on placebo. Lymphocyte and neutrophil counts were not obtained after the first infusion in Study 2.
 - Infusion-related reactions can occur during the infusion or after completion of the infusion. In the event of an infusion-related reaction during the infusion, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy started as clinically indicated. Consider prophylactic treatment with antihistamines, acetaminophen, NSAIDs, or corticosteroids prior to future infusions.

• Common adverse drug reactions:

- Listed % incidence for adverse drug reactions= reported % incidence for drug (Leqembi IV) minus reported % incidence for placebo in Study 1. Please note that an incidence of 0% means the incidence was the same as or less than placebo.
 - The most frequently reported adverse events included infusion-related reactions (17%), headache (4%), ARIA-E (9%), cough (4%), and diarrhea (3%).
- Listed % incidence for adverse drug reactions= reported % incidence for drug (Leqembi IV) minus reported % incidence for placebo in Study 2. Please note that an incidence of 0% means the incidence was the same as or less than placebo.
 - The most frequently reported adverse events included infusion-related reactions (19%), ARIA-H (6%), ARIA-E (11%), headache (3%), superficial siderosis of CNS (3%), rash (2%), and nausea/vomiting (2%).
 - Note that rash includes acne, erythema, infusion site rash, injection site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

• **Drug interactions:** None.

• **Special populations:**

- There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.
- The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Alzheimer's dementia is a neurodegenerative disease described as a slow development of cognitive and memory impairment. It generally involves older adults who are 65 years of age or older and it impedes daily activities and function (*Bennett et al 2025, Wolk and Dickerson 2024*).
- Leqembi is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with Leqembi should be initiated in patient with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.
 - Confirm the presence of amyloid beta pathology and obtain a recent baseline brain MRI prior to starting treatment.
- Leqembi (lecanemab-irmb) for intravenous infusion was FDA approved in 2023. Leqembi Iqlik for subcutaneous administration was FDA approved in 2025.
 - Initiate treatment with Leqembi IV infusion; after 18 months, the starting dosage may be continued or a transition to maintenance dosage regimen may be considered, which can be administered by either IV infusion (once every 4 weeks) or SC injection (once every week).
- Leqembi has a box warning regarding amyloid related imaging abnormalities.
 - Consider the benefit of Leqembi for the treatment of AD and potential risk of serious adverse events associated with ARIA when deciding to start treatment with Leqembi.
- The efficacy of Leqembi was assessed in two double-blind, placebo-controlled, parallel-group studies that compared the IV formulation with placebo.
 - The primary endpoint of Study 1 was the change from baseline on a weighted composite score consisting of selected items from the CDR-SB, MMSE, and ADAS-Cog14 at week 53.
 - Leqembi had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at week 53, which did not meet the prespecified success criterion of 80%.
 - The primary efficacy outcome of Study 2 was the change from baseline at 18 months in the CDR-SB.

- Leqembi met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared to placebo at 18 months ($p < 0.0001$).
- Using population pharmacokinetic modeling and simulation, the intravenous (10mg/kg once every 4 weeks) and subcutaneous (360mg once weekly) maintenance dosing regimens of lecanemab-irmb were predicted to have similar pharmacokinetic exposure.
- There are currently no US treatment guidelines found for AD or that include Leqembi. Comparator treatment with Leqembi includes Kisunla.

- There is no evidence to suggest that Leqembi is safer or more effective than other disease modifying agents for Alzheimer’s disease. It is therefore recommended that Leqembi remain non-preferred and require prior authorization to determine clinical diagnosis and parameters of use.

- **PDL Placement:**
 - Preferred
 - Non-Preferred

References

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