

Lecanemab (Leqembi®) in Early Alzheimer's Disease

A Clinical Guide for Family Physicians in Canada

ABSTRACT

Lecanemab (Leqembi®), approved by Health Canada in October 2025, represents Canada's first disease-modifying therapy for Alzheimer's disease. This guide reviews patient selection criteria, including mandatory APOE genotyping and amyloid biomarker confirmation, for adults with mild cognitive impairment or mild dementia due to Alzheimer's disease. Key safety considerations include amyloid-related imaging abnormalities (ARIA), requiring rigorous MRI surveillance protocols. Family physicians play essential roles in early identification, coordinating pre-treatment workups, monitoring for adverse events, and providing collaborative care throughout treatment.

KEYWORDS: Lecanemab, Alzheimer's disease, amyloid-related imaging abnormalities (ARIA), APOE genotyping, disease-modifying therapy

Alzheimer's disease (AD) affects over 771,000 Canadians, with projections exceeding 1 million by 2030.[1] On October 25, 2025, Health Canada issued a Notice of Compliance with Conditions (NOC/c) for lecanemab (brand name Leqembi®), marking a historic milestone as the first disease-modifying therapy for AD approved in Canada.[2]

Lecanemab is a humanized IgG1 monoclonal antibody that selectively binds to soluble amyloid-β (Aβ) aggregates (protofibrils) and insoluble Aβ fibrils, reducing both protofibrils and plaques in the brain.[3] Unlike symptomatic treatments such as cholinesterase inhibitors, lecanemab targets an underlying pathological mechanism of AD.

As a family physician, you play a critical role in identifying potential candidates, facilitating referrals, and providing ongoing care. This guide outlines the clinical criteria,



D'Arcy Little, MD, CCFP, FCFP, FRCPC, *Medical Director, Journal of Current Clinical Care and www.healthplexus.net Radiologist, Orillia Soldiers' Memorial Hospital, Assistant Professor, Department of Medical Imaging cross-appointed to Department of Family and Community Medicine, University of Toronto, University of Toronto, Toronto, ON.*

KEY POINTS FOR PRIMARY CARE

- Health Canada approved lecanemab (Leqembi®) on October 25, 2025—Canada's first disease-modifying Alzheimer's therapy
- Indicated for MCI or mild dementia due to AD with confirmed amyloid pathology
- Requires APOE genotyping – excluded for homozygous ε4 carriers in Canada
- MRI monitoring essential: baseline plus scheduled follow-up for ARIA detection
- Provincial coverage and pricing remain to be determined

workup requirements, imaging protocols, and safety monitoring essential for collaborative management of patients on lecanemab therapy.

Mechanism of Action

Lecanemab preferentially targets Aβ protofibrils—soluble oligomeric aggregates considered highly neurotoxic—with additional activity against fibrillar amyloid plaques. In the CLARITY-AD Phase 3 trial, treatment resulted in a 59% reduction in brain amyloid burden at 18 months compared to placebo, as measured by amyloid PET imaging.[3,4] The drug is administered as an intravenous infusion (10 mg/kg) every two weeks.

Patient Selection and Diagnostic Criteria

Clinical Eligibility

Lecanemab is indicated for adults with a clinical diagnosis of mild cognitive impairment (MCI) or mild dementia due to AD who meet the following criteria:[2,5]

APOE Genotyping

APOE genotyping is mandatory before initiating therapy. In Canada (and Europe), lecanemab is contraindicated in APOE ε4

Inclusion Criteria	Exclusion Criteria
• Age 50–90 years • MMSE score 22–30 • Clinical diagnosis of MCI due to AD or mild AD dementia • Confirmed amyloid pathology (PET or CSF) • APOE ε4 non-carrier or heterozygote	• APOE ε4 homozygous (ε4/ε4) • Moderate or advanced dementia • ≥5 cerebral microbleeds on MRI • Any macrohemorrhage (>10mm) • Cortical superficial siderosis • Recent stroke/TIA (within 12 months) • Anticoagulant therapy • Uncontrolled seizure disorder

homozygotes due to significantly elevated ARIA risk (approximately 5.6-fold higher incidence of ARIA-E compared to non-carriers).[6,7] Heterozygous carriers may proceed with enhanced monitoring.

Pre-Treatment Diagnostic Workup

Confirming Amyloid Pathology

Biomarker confirmation of brain amyloid is required prior to initiating treatment. Two modalities are accepted:[5,8]

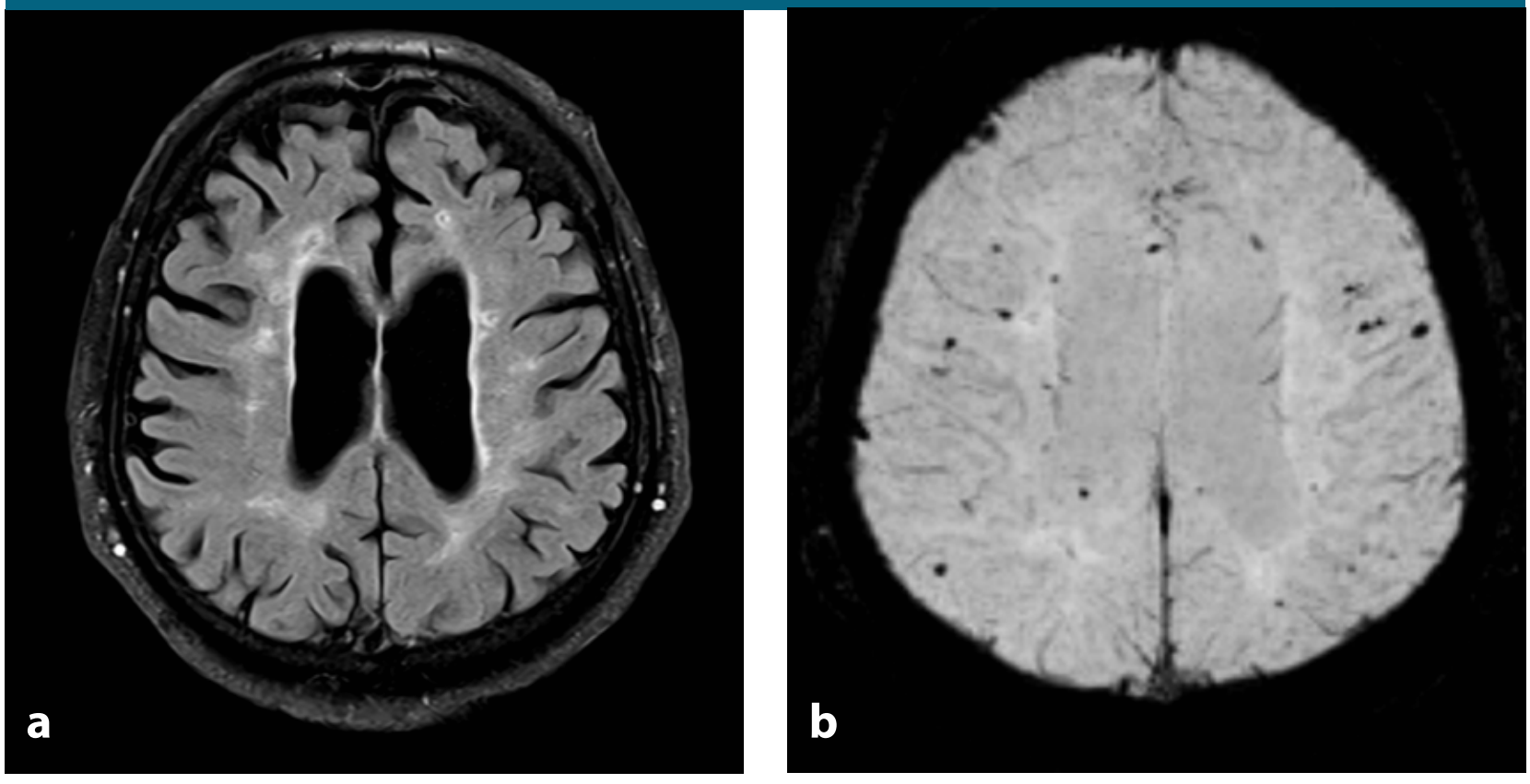
1. **Amyloid PET imaging:** Provides direct visualization of amyloid plaque burden. Considered the reference standard in clinical trials. A positive scan shows tracer retention in cortical gray matter consistent with moderate-to-high amyloid deposition.
2. **CSF biomarkers:** Reduced Aβ42 (or Aβ42/Aβ40 ratio) combined with elevated phosphorylated tau (p-tau181 or p-tau217) and/or total tau. CSF analysis via lumbar puncture offers comparable diagnostic accuracy to PET and may be more accessible in some centres.

Emerging blood-based biomarkers: Plasma p-tau217 and Aβ42/40 assays show promise for screening but are not yet approved in Canada for treatment eligibility determination.

Baseline MRI Requirements

A brain MRI within 12 months prior to treatment initiation is mandatory to:[9,10]

Figure 1: Axial T2 FLAIR and GRE Imaging of the Brain



a. T2 images show atrophy and white matter microangiopathic changes.
b. GRE images show multiple foci of blooming on Gradient Echo, compatible with amyloid angiopathy, a contraindication to Lecanemab treatment.

- Exclude alternative causes of cognitive impairment (e.g., normal pressure hydrocephalus, subdural hematoma, tumor)

ARIA-E (Edema/Effusion)

Imaging Features:

- Vasogenic edema appearing as increased signal intensity on T2-FLAIR sequences
- Sulcal effusion (hyperintense fluid in the subarachnoid space)
- Typically involves cortical and subcortical regions
- No restricted diffusion on DWI (differentiates from cytotoxic edema/infarction)
- Usually transient and resolves over 2–4 months

Incidence: ~12.6% in CLARITY-AD trial; most cases (≈75%) asymptomatic[4]

Timing: Most common in first 3 months of treatment (peak: weeks 5–14)

ARIA-H (Hemosiderosis/Microhemorrhages)

Imaging Features:

- Cerebral microbleeds: punctate hypointense foci (≤10mm) on T2*-GRE or SWI
- Superficial siderosis: linear hypointensity along cortical surface/sulci
- Lobar distribution typical (frontal, parietal, temporal cortex)
- May be permanent (hemosiderin deposits persist)

Incidence: ~17% in CLARITY-AD trial (includes pre-existing lesions)[4,14]

Clinical significance: Most are radiographically mild and asymptomatic

- Assess for pre-existing hemorrhagic lesions that may preclude treatment
- Establish baseline for ARIA monitoring
- Document degree of white matter hyperintensity and cerebral atrophy

Amyloid-Related Imaging Abnormalities (ARIA)

ARIA represents the most significant safety consideration with anti-amyloid monoclonal antibody therapy. The term was coined by the Alzheimer's Association Research Roundtable in 2011 to describe a spectrum of MRI findings observed during amyloid-targeting treatment.[11,12]

Pathophysiology

ARIA is believed to result from treatment-induced mobilization of amyloid deposits from cerebral blood vessel walls. When monoclonal antibodies bind to vascular amyloid, they trigger local inflammation and transiently increase vascular permeability, leading to extravasation of proteinaceous fluid (ARIA-E) or blood products (ARIA-H).[12,13] The pathophysiology shares features with cerebral amyloid angiopathy-related inflammation (CAA-ri).

ARIA Classification

ARIA comprises two distinct imaging phenotypes:

⚠ CRITICAL SAFETY ALERT

Patients on lecanemab presenting to the emergency department with stroke-like symptoms should **NOT** receive thrombolytic therapy (tPA) until ARIA has been excluded by MRI. At least one fatality has been reported following tPA administration in a patient with ARIA-related hemorrhage.[16]

Always communicate lecanemab treatment status to emergency personnel.

Clinical Presentation of ARIA

The majority of ARIA cases (approximately 75–80%) are asymptomatic and detected only on surveillance MRI. When symptoms occur, they may include:[10,15]

- Headache (most common symptomatic presentation)
- Confusion or altered mental status
- Visual disturbances
- Dizziness, nausea
- Gait difficulty

ARIA SEVERITY CLASSIFICATION

Severity	ARIA-E Criteria	ARIA-H Criteria
Mild	<5 cm greatest dimension; 1 location	≤4 new microbleeds; 1 focal siderosis
Moderate	5–10 cm; or 2–4 locations	5–9 new microbleeds; 2 focal siderosis
Severe	>10 cm; or >4 locations	≥10 new microbleeds; >2 disseminated siderosis

MRI PROTOCOL FOR ARIA MONITORING

Essential sequences

The minimum recommended MRI protocol for ARIA assessment includes:[9,17]

Sequence	Primary Purpose	Key Parameters
T2-FLAIR	ARIA-E detection (edema, sulcal effusion)	3D acquisition preferred; ≤3mm slice thickness
T2* GRE	ARIA-H detection (microbleeds, siderosis)	TE ≥20ms for optimal sensitivity
DWI	Differentiate ARIA-E from acute infarct	Include ADC map
3D T1	Anatomical reference; volumetric analysis	1mm isotropic preferred

Note on SWI vs. T2* GRE: SWI sequences detect approximately 3× more microbleeds than standard T2* GRE due to increased sensitivity. However, CLARITY-AD eligibility and monitoring criteria were established using T2* GRE with TE ≥20ms. Until equivalence thresholds are validated, centers should maintain consistency between baseline and follow-up protocols.[17,18]

MONITORING SCHEDULE

The following MRI surveillance schedule is recommended:[10,19]

Timing	Approximate Week	Purpose
Before infusion #3	Week 4	Early detection (FDA 2025 update)
Before infusion #5	Week 8	Peak ARIA-E risk period
Before infusion #7	Week 12	Continued early monitoring
Before infusion #14	Week 26	Mid-treatment surveillance
Before infusion #26	Week 52	Annual review

Unscheduled MRI: Any new neurological symptoms (headache, confusion, visual changes, seizure, focal deficits) warrant urgent MRI evaluation.

- Seizures (rare but serious; status epilepticus has been reported)

Clinical Efficacy

The CLARITY-AD Phase 3 trial enrolled 1,795 participants with early AD (MCI or mild dementia with confirmed amyloid). At 18 months, lecanemab demonstrated:[4]

- **Primary endpoint:** 27% relative reduction in decline on CDR-SB (Clinical Dementia Rating–Sum of Boxes) compared to placebo (absolute difference: 0.45 points; 95% CI 0.27–0.63; p<0.001)
- **Brain amyloid:** 59% greater reduction in amyloid plaque burden (amyloid PET)
- **Functional outcomes:** 37% relative reduction in decline on ADCS-MCI-ADL (instrumental activities)
- **Cognition:** 26% relative reduction in decline on ADAS-Cog[14]

Clinical interpretation: While statistically significant, debate continues regarding the clinical meaningfulness of observed differences. The 0.45-point difference on CDR-SB represents approximately 4–5 months of delayed progression over 18 months. The Canadian Consortium on Neurodegeneration in Aging (CCNA) notes that effects on cognition were proportionally smaller than effects on amyloid clearance, warranting further research.[20]

Canadian Context and Access

Health Canada's approval represents an important first step, but several challenges remain for implementation:[2,20]

1. **Provincial coverage:** Drug plans have not yet made reimbursement decisions. Review by Canada's Drug Agency (CDA-AMC) is ongoing.

SUMMARY OF KEY POINTS

- **Patient Selection:** Indicated for adults aged 50-90 with MCI or mild dementia due to Alzheimer's disease, confirmed amyloid pathology (PET or CSF), and MMSE 22-30. APOE ε4 homozygotes excluded due to elevated ARIA risk.
- **Pre-Treatment Requirements:** Mandatory APOE genotyping, amyloid confirmation, and baseline MRI. Patients with ≥5 microbleeds, macrohemorrhage, superficial siderosis, or anticoagulant use are excluded.
- **ARIA Monitoring:** Imaging abnormalities occur in 13% (edema) and 17% (hemorrhage) of patients, mostly asymptomatic. MRI surveillance required at weeks 4, 8, 12, 26, and 52.
- **Clinical Efficacy:** 27% relative reduction in cognitive decline at 18 months, representing approximately 4-5 months of delayed progression compared to placebo.

2. **Pricing:** Canadian pricing not finalized. US reference price is approximately $26,500 USD annually.
3. **Infrastructure:** Access to amyloid PET, specialized memory clinics, and MRI capacity varies significantly across provinces.
4. **Specialty care:** Treatment requires coordination between neurologists/geriatricians, radiologists, infusion centres, and primary care.
5. **CCNA resources:** The Canadian Consortium on Neurodegeneration in Aging has published comprehensive guidance on implementation challenges and research priorities.

Role of the Family Physician

Family physicians serve as essential partners in the lecanemab care pathway:

1. **Early identification:** Screen for cognitive symptoms; use validated tools (MoCA, MMSE); refer early for specialist evaluation
2. **Pre-treatment workup:** Coordinate basic investigations (CBC, metabolic panel, TSH, B12); order

CLINICAL PEARLS

NO tPA with ARIA: Patients presenting with stroke-like symptoms should NOT receive thrombolytics until ARIA excluded by MRI. Always alert emergency personnel to lecanemab treatment status.

Anticoagulation Excludes Treatment: All anticoagulant therapy is contraindicated. Review antiplatelet medications during pre-treatment assessment.

ARIA is Usually Silent: 75-80% of cases are asymptomatic. Maintain high suspicion for headache, confusion, or visual changes in first 3 months when risk peaks.

baseline MRI if requested

3. **Risk factor assessment:** Review anticoagulant/antiplatelet use; assess cardiovascular and bleeding risk
4. **Ongoing monitoring:** Monitor for interval symptoms; reinforce MRI attendance; manage comorbidities
5. **Family support:** Counsel caregivers; connect with Alzheimer Society resources; discuss goals of care
6. **ARIA vigilance:** Maintain high index of suspicion for new neurological symptoms; communicate treatment status to emergency personnel

Summary

Lecanemab represents a paradigm shift in Alzheimer's disease treatment, moving from symptomatic management to disease modification. While the magnitude of clinical benefit continues to be debated, the approval offers hope for patients in the early stages of disease. Careful patient selection, rigorous MRI monitoring for ARIA, and collaborative care between specialists and primary care physicians will be essential for optimizing outcomes and ensuring patient safety as this therapy becomes available in Canada.

This article is intended for educational purposes. Clinical decisions should be made in consultation with specialist colleagues and according to local guidelines.

References

1. Alzheimer Society of Canada. Dementia numbers in Canada. Available at: https://alzheimer.ca/en/about-dementia/what-dementia/dementia-numbers-canada
2. Health Canada. Notice of Compliance with Conditions for Leqembi (lecanemab). October 25, 2025.
3. Swanson CJ, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab. Alzheimers Res Ther. 2021;13:80.
4. van Dyck CH, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023;388:9-21.
5. Cummings J, et al. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2023;10:362-377.
6. NCBI Bookshelf. Lecanemab Therapy and APOE Genotype. Medical Genetics Summaries. 2024.
7. Suh CH, et al. Incidence of Amyloid-Related Imaging Abnormalities in Phase III Clinical Trials. Neurology. 2025.
8. Jack CR Jr, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14:535-562.
9. Jeong SY, et al. Amyloid-Related Imaging Abnormalities in the Era of Anti-Amyloid Beta Monoclonal Antibodies. Korean J Radiol. 2024;25:726-741.
10. Cogswell PM, et al. Alzheimer Disease Anti-Amyloid Immunotherapies: Imaging Recommendations. AJNR Am J Neuroradiol. 2025;46:24-32.
11. Sperling RA, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials. Alzheimers Dement. 2011;7:367-385.
12. Hampel H, et al. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. Brain. 2023;146:4414-4424.
13. Barakos J, et al. MR Imaging Features of Amyloid-Related Imaging Abnormalities. AJNR Am J Neuroradiol. 2013.
14. Agarwal A, et al. Amyloid-related Imaging Abnormalities in Alzheimer Disease Treated with Anti–Amyloid-β Therapy. RadioGraphics. 2023;43:e230009.
15. Martinez SA, et al. Amyloid-related imaging abnormalities (ARIA): diagnosis, management, and care. J Am Coll Emerg Physicians Open. 2024.
16. Solopova E, et al. Fatal iatrogenic cerebral β-amyloid-related arteritis. Nat Commun. 2023;14:8220.
17. Korean Society of Neuroradiology. Amyloid-Related Imaging Abnormalities: Expert Recommendation for Standard MRI Protocol. 2025.
18. French Federation of Memory Clinics. Lecanemab for early Alzheimer's disease: Appropriate use recommendations. 2025.
19. FDA. Additional, earlier MRI monitoring for patients taking Leqembi. Drug Safety Communication. 2025.
20. Smith EE, et al. Use of lecanemab and donanemab in the Canadian healthcare system: Evidence, challenges, and areas for future research. J Prev Alzheimers Dis. 2025.