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Viewpoint

When It Comes to Lecanemab (and Donanemab), How Might We Think about 'Reasonable and Necessary'?

L.S. Schneider

Corresponding Author: Lon S. Schneider, MD, Keck School of Medicine of USC, Los Angeles, USA, lschneid@usc.edu

In principle, an insurance underwriter like the US government's Center for Medicare and Medicaid Services (CMS) should cover treatments that work and not cover those that don't. Nevertheless, many treatments that don't work very well are ensconced in medical practice and paid for by insurance. Cholinesterase inhibitors and memantine are covered by CMS for treating Alzheimer's disease based on clinical trials for efficacy and safety and FDA marketing approval despite the many individuals and organizations who consider that their clinical effects are trivial. Although their reimbursement was restricted when first marketed in the 1990s, they weathered the test of time, are available as very cheap generic drugs, and often don't have a required co-pay. Initial broadly expressed controversy about their uses has settled over their three decades of clinical use even for off-label use. For example, memantine is commonly used for mild dementia and MCI where there is little or no substantial evidence for its effectiveness, and insurance tends to pay. Newer FDA approved formulations such as fixed combinations of donepezil and memantine or a donepezil transdermal patch, are also reimbursed by CMS despite their high price and absent evidence that they are more effective than original formulations.

Both FDA and CMS show flexibility here and for different reasons. For the FDA, guidelines allow for not having to directly assess effectiveness of new formulations and combination products. For CMS it involves both a concept of 'reasonable and necessary,' as well as cost and demand.

FDA's marketing approval for most treatments largely meets CMS's regulation that a covered treatment must be 'reasonable and necessary' if the approval is based on the 'substantial evidence' requirement. For CMS, 'reasonable and necessary' means the treatment: (1) meets FDA's 'substantial evidence' standard, (2) is not experimental, and (2) is appropriate for Medicare patients (42 CFR § 405.201(b)).

For the FDA 'substantial evidence' for effectiveness means:

> "[E]vidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that *the drug will have the effect it purports or is represented to have under the conditions of use prescribed*, recommended, or suggested in the labeling…." [Italics added]. (The FD&C Act 505(d) (21 U.S.C. § 355(d)))

Aducanumab was given accelerated approval, largely, because it did not meet 'substantial evidence' criteria. Rather, its ability to reduce amyloid plaques was the basis for approval, not effectiveness; and consequently, CMS couldn't see it as a 'reasonable and necessary' treatment. Lecanemab, however, is likely to receive regular marketing approval, precisely because, on face, it meets 'substantial evidence' criteria. Therefore, it is likely to be covered under Medicare after FDA approval. (It helps that the US Veteran's Affairs health system already covers it).

In brief, what the US government considers 'reasonable and necessary' may not be what a clinician, patient, family, advocacy group, or charity think when they consider what's 'reasonable and necessary.' For the government and insurance companies, it is a legal term. Consumers likely interpret it more impressionistically.

Physicians may believe that they don't do other than what is reasonable and necessary. Lecanemab will test this premise as it enters clinical practice with great expectations, hope, hype, skepticism, and perhaps temerity. A very small statistical effect of uncertain clinical meaning, accompanied by substantial rates of potentially serious adverse effects, requiring compliance with a time-intensive clinical regimen, and that is costly whether or not it is covered by Medicare, pose formidable barriers to lecanemab's use.

Many patients will learn about Leqembi™ through direct-to-consumer advertising. Substantial pressure for clinical use may come from patient advocacy organizations and charities in the context of increasing donations and lobbying the government. Will this be a main driver for lecanemab? In the early stages of the marketing of Aduhelm® it appeared as though the pharmaceutical company and the advocacy organizations were promoting specialized antibody clinics. With regular FDA approval of lecanemab will demand come organically from patients themselves, their families,

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or perhaps be stimulated by the direct-to-consumer advertising? Will physicians approach their own patients to suggest treatment?

Whatever way patients are recruited, a challenge is qualifying them for treatment as lecanemab is indicated for only a narrow slice of the Alzheimer's spectrum, i.e., those with MCI or mild Alzheimer's disease confirmed by a positive amyloid-PET scan or amyloid/tau CSF marker, an MMSE ≥ 22, and documented impaired memory. Unfortunately, most Alzheimer patients seeking treatment will be too cognitively impaired or have too uncertain amyloid pathology to qualify. Some will have a positive amyloid PET and subjective memory complaints. Physicians will be tempted to treat these patients despite the indications in the label. All this impacts on what 'reasonable and necessary' really means.

Major barriers to broad usage are realized in the clinic where substantial effort will be made to qualify a patient medically, socially, culturally, and financially. Does the patient have early Alzheimer disease confirmed by an amyloid biomarker, are they medically relatively healthy, do not have preexisting brain lesions, cardiovascular illness, or other medical contraindications? Is their cognitive impairment in just the right spot, not too unimpaired or impaired? Do they have family to help with treatment?

Explaining the potential for attenuating cognitive decline may be difficult for patients to understand or flat out misleading. We are offering hope that the very small, 0.45 difference in CDR-SB between treatment and placebo will grow with time. Physicians must explain the high risks for ARIA and its consequences, explaining that the vast majority of ARIA is asymptomatic and will resolve completely over a few months. But will patients hear they may have to stop treatment, have a certain low chance of severe or 'serious' edema and hemorrhage that could require hospitalization?

Charges for lecanemab treatment may run to $90K per year, including medication, infusions, MRIs, PET, laboratory tests, medical visits, and other services. If Medicare covers all this, then there still would be a substantial co-pay of about 20%. Here, patients and families must understand the commitment in time, energy, and treasure; must balance expectations, and decide for themselves whether anti-amyloid antibody treatment is reasonable and necessary. What's 'reasonable and necessary' can be uncertain business.

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