Leqembi™ (lecanemab-irmb) for Alzheimer's disease – New drug approval

- On January 6, 2023, the FDA announced the approval of Eisai and Biogen's Leqembi (lecanemab-irmb), for the treatment of Alzheimer's disease (AD). 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. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.

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

- AD is an irreversible, progressive brain disorder affecting more than 6.5 million people in the U.S. While the specific causes of AD are not fully known, it is characterized by changes in the brain – including amyloid beta plaques and neurofibrillary, or tau, tangles.

- Leqembi is the second FDA approved biologic therapy for AD targeting amyloid beta. In June 2021, the FDA approved Aduhelm™ (aducanumab), the first amyloid beta-directed antibody, via the accelerated approval pathway based on reductions in amyloid beta plaques. However, because of unknown clinical benefit (eg, improvement in progression of disease), CMS issued a National Coverage Determination that limited Medicare coverage for Aduhelm to patients enrolled in clinical trials.

- The accelerated approval of Leqembi was based on a randomized, double-blind, placebo-controlled, dose finding study (Study 1) in 856 patients with AD and mild cognitive impairment or mild dementia stage of disease. Patients were randomized to receive one of 5 doses (161 of which were randomized to the recommended dosing regimen of 10 mg/kg every two weeks) of Leqembi or placebo. The primary endpoint was change from baseline on a weighted composite score consisting of selected items from the Clinical Dementia Rating-Sum of Boxes (CDR-SB), Mini-Mental State Examination (MMSE), and AD Assessment Scale - Cognitive Subscale 14 (ADAS-Cog 14) at week 53. A key secondary endpoint was reduction in brain amyloid plaque, using positron emission tomography (PET) imaging, from baseline to week 79.

    — Leqembi failed to meet the primary endpoint; however, a statistically significant reduction in brain amyloid plaque from baseline to week 79 was observed with Leqembi compared to the placebo arm, which had no reduction of amyloid beta plaque.

- The results of Clarity AD, the confirmatory Phase 3 trial for Leqembi have recently been reported, and the FDA anticipates receiving the data soon. If the FDA review is positive, this could convert the accelerated approval to a full (traditional) approval, potentially by the end of 2023.

- Warnings and precautions for Leqembi include amyloid related imaging abnormalities (ARIA) and infusion-related reactions.

    — ARIA can be asymptomatic but serious and life-threatening events rarely may also occur. ARIA most commonly presents as temporary swelling in areas of the brain that usually resolves over time and may be accompanied by small spots of bleeding in or on the surface of the brain; some people may have symptoms such as headache, confusion, dizziness, vision changes, nausea, and seizure.
    — Leqembi dosing may need to be suspended if symptoms of ARIA develop.

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- The most common adverse reactions (at approximately 10% and higher incidence compared to placebo) with Leqembi use were infusion-related reactions, headache, and ARIA-edema.

- The recommended dosage of Leqembi is 10 mg/kg administered as an intravenous infusion over approximately one hour, once every two weeks.

    — The presence of amyloid beta pathology should be confirmed prior to initiating treatment.
    — To monitor for ARIA, a recent (within one year) brain MRI should be obtained prior to initiating treatment with Leqembi. An MRI should then be obtained prior to the 5th, 7th, and 14th infusions.

- The estimated price of Leqembi is $26,500 per year (estimated annual price based on 10 mg/kg IV biweekly for average U.S. patient weight of 75 kg).

- Leqembi will be available during or before the week of January 23, 2023.

- Leqembi will be available as a 500 mg/5 mL and 200 mg/2 mL solution in single-dose vials.

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