OPTUMRx®

Aduhelm™ (aducanumab) – New drug approval

- On June 7, 2021, the FDA announced the approval of Biogen's Aduhelm (aducanumab), for the treatment of Alzheimer's disease.
    - This is an accelerated approval based on reductions 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). No timeline is available for the completion of the confirmatory trial.

- Alzheimer's is an irreversible, progressive brain disorder that slowly destroys memory and cognition. While the specific causes of Alzheimer's disease are not fully known, it is characterized by changes in the brain - including amyloid plaques and neurofibrillary, or tau, tangles - that result in loss of neurons and their connections.
    - Alzheimer's affects 6.2 million people in the U.S.

- Aduhelm is a first-in-class human monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. Aduhelm is the first therapy to target the underlying pathophysiology of the disease.

- A complete description of the clinical efficacy data can be found in the prescribing information, but the key points include:
    - The efficacy of Aduhelm was based upon two double-blind, randomized, placebo-controlled, studies (N = 1,638 for study 1; N = 1,647 for study 2) in patients with Alzheimer's disease and mild cognitive impairment or mild dementia stage of disease.
    - The primary efficacy endpoint was the change from baseline on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) at week 78.
    - Studies 1 and 2 were terminated prior to their planned completion due to futility. Study endpoints were later analyzed according to the prespecified statistical analysis plan and the efficacy signal prompted Biogen to file for FDA approval.
    - In study 1, high dose Aduhelm was associated with statistically significant change from baseline in CDR-SB compared to placebo (treatment difference of -0.39 [-22%], p = 0.0120). Low dose Aduhelm was numerically better than placebo, but the difference was not statistically significant.
    - In study 2, No statistically significant differences were observed between the Aduhelm-treated and placebo-treated patients for the CDR-SB endpoint.

- A subgroup of patients from Studies 1 and 2 were evaluated for changes in key biomarkers using positron emission tomography (PET) and cerebrospinal fluid assays. Individuals receiving high dose Aduhelm demonstrated significant reductions in beta amyloid plaques compared with placebo.
    - This reduction in beta amyloid, a surrogate marker for Alzheimer's disease pathology, was the basis for accelerated approval.
    - Per the FDA, a surrogate endpoint is a marker that is thought to predict clinical benefit but is not itself a measure of clinical benefit.

- The approval of Aduhelm comes after an FDA Advisory Committee reviewed the drug in November 2020. The Committee did not endorse Aduhelm. Of the 11 voting members, 10 voted that they did not think study 1 (the single trial indicating benefit as measured by CDR-SB) could be used as primary evidence of effectiveness of Aduhelm (1 panelist was uncertain).

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- Warnings and precautions for Aduhelm include amyloid-related imaging abnormalities (ARIA) and hypersensitivity reactions.

- The most common adverse reactions (> 10% and higher incidence compared to placebo) with Aduhelm use were ARIA-edema (ARIA-E), headache, ARIA-hemosiderin deposition (ARIA-H) microhemorrhage, ARIA-H superficial siderosis, and fall.

- After an initial titration, the recommended dosage of Aduhelm is 10 mg/kg (see table below for titration schedule). Aduhelm is administered as an intravenous (IV) infusion over approximately one hour every 4 weeks and at least 21 days apart.

IV infusion (every 4 weeks)	Aduhelm dosage
Infusion 1 and 2	1 mg/kg
Infusion 3 and 4	3 mg/kg
Infusion 5 and 6	6 mg/kg
Infusion 7 and beyond	10 mg/kg

  - Because of the risk of developing ARIA, a recent (within one year) MRI should be obtained prior to initiating Aduhelm.
  - MRIs prior to the 7th infusion and 12th infusion should also be obtained. If significant changes are observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (ie, no increase in size or number of ARIA-H).
  - Refer to the Aduhelm drug label for complete dosing and administration recommendations.

- The wholesale acquisition cost (WAC) of Aduhelm is $4,312 per infusion for a 74 kg patient (the average weight of a U.S. patient with mild cognitive impairment or mild dementia). The yearly cost at the maintenance dose (10 mg/kg) would be $56,000.

  - The cost during the first year of treatment will be lower due to the titration period.

- Biogen's plans to launch Aduhelm in the next 2 – 3 weeks.

  - Aduhelm will be available as a 170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL) solution in single-dose vials.

Action Plan

- First Mover: Due to the potential for cost and utilization impact to a client's pharmacy budget, Aduhelm was identified as a "First Mover" pipeline drug and reviewed by the OptumRx P&T committee prior to FDA approval. Preliminary utilization management criteria was discussed by the P&T Committee, preliminarily approved, and is available for implementation upon launch of Aduhelm.

- Formulary Coverage: Aduhelm will be added to the New Drugs to Market list, which excludes certain new drugs upon launch providing clients extra time to determine their approach. Aduhelm will be excluded from the Select and Premium formularies for up to 6 months for clients who have elected this program.

- For all other Select formulary clients, Aduhelm will default to the highest tier upon launch. Aduhelm will also be initially excluded on the Premium Value formulary and OptumRx Medicare formularies. OptumRx will evaluate further utilization management and exclusion strategies based on the recommendations from OptumRx's independent P&T committee.

- P&T Review: Aducanumab was reviewed by the OptumRx P&T committee in February 2021 after the FDA advisory committee and before the FDA approval decision.

- Now that the FDA has approved Aduhelm, it will be reviewed again at the next P&T committee meeting in July 2021 to consider the FDA approved label and any new information not included in the original P&T committee review, to confirm utilization management strategy, and to establish the drug designation which guides formulary placement. Strategies such as exclusions and stringent utilization management criteria are in place to manage Aduhelm for clients that choose.

- Medical Benefit: Since Aduhelm is an infused therapy with additional administration and diagnostic testing needs it will primarily be adjudicated under the medical benefit. OptumRx recommends that clients consider limiting coverage of Aduhelm to the medical benefit.

- Information regarding Aduhelm will be posted on the optumrx.com portals.