Aduhelm: Restrictive Coverage Finalized

Good News for Future Therapies (LLY, ROG)

This evening CMS released a final NCD for Alzheimer's therapy, Aduhelm, as well as the rest of the class (here). The new policies are effective immediately.

- **Medicare will cover monoclonal antibodies (mAbs) that target amyloid (or plaque) for Alzheimer's disease that receive FDA approval under coverage with evidence development (CED).** CMS will provide enhanced access and coverage for people with Medicare participating in CMS-approved studies, such as a data collection through routine clinical practice or registries. Registry data may be used to assess whether outcomes seen in carefully controlled clinical trials (e.g., FDA trials) are reproduced in the real-world and in a broader range of patients.

- **Restrictive coverage remains largely as proposed.** Any new drugs in this class that receive FDA traditional approval may be available in additional care settings that people with Medicare can use, such as an outpatient department or an infusion center. **Future drugs will be covered in a similar fashion (i.e., accelerated approval)**. Secondly, for drugs that FDA has not determined to have shown a clinical benefit (or that receive an accelerated FDA approval), Medicare will cover in the case of FDA or National Institutes of Health (NIH) approved trials. **PET would be covered in these (limited) circumstances.** Under this NCD, CMS will support the FDA by covering the drug and any related services (including, in some cases, PET scans if required by trial protocol) for people with Medicare who are participating in these trials.

- **However the NCD is good news for future therapies (LLY, ROG) as real-world evidence may be used (registry).** The CMS provides a coverage playbook for future therapies. Should future Alzheimer's drugs that also target the amyloid proteins thought to cause the disease drugs undergo a traditional approval process -- not the accelerated approval process -- patients would not need to be in a randomized, controlled trial. Instead, they could be in a patient registry, which tracks how patients fare when they receive the drug. Unlike a randomized trial, it doesn't require any patient to receive a placebo.

- **Now what? Part B premiums will surely come down now.** HHS Secretary Becerra will ask CMS to lower the Part B premium in '22 given the price hike was 50% due to Aduhelm. The drug was originally priced at $56K per year. BIIB announced a priced reduction to $28K per year at the end of December 2021. While BIIB stated the initial price was based on real world evidence, the company acknowledges virtually no one agreed with the price.

- **NEXT UP: The NCD is effective immediately. Part B premiums will come down. More broadly, the FDA Accelerated Approval pathway will be reformed via FDA User Fee bill this fall.** BIIB stated it anticipates 2022 accelerated approval for its anti-amyloid product Lecanemab under Breakthrough Designation, but it could face pushback similar to Aduhelm's. We note that LLY and other competitors will surpass BIIB as the company struggles to maintain its position as a leader in Alzheimer's care. Notably LLY has set up a head to head trial comparing its donanemab with BIIB's Aduhelm to test both drugs' abilities to clear amyloid plaques and improve cognition in Alzheimer's patients. Data to date shows LLY's donanemab outperforms Aduhelm. FDA has already granted donanemab Breakthrough Therapy designation, paving the way for timely approval once the company submits comprehensive clinical trial data.

Contact Ipsita Smolinski - 202.250.3741 - Ipsita@capitol-street.com

Background

From Proposed NCD:

- **The CMS CED covers an entire class of drugs, not only Aduhelm (BIIB, LLY, ROG, ESALY).** CMS's CED covers all antiamyloid-beta monoclonal antibodies (antiamyloid mAbs), laboratory-made proteins designed to act as binders that activate the body's immune system. Scientists design mAbs as treatments for clearing amyloid plaque accumulation in Alzheimer's patients. Aduhelm is the first and only antiamyloid mAb with FDA approval. This CED is a positive for companies with Alzheimer's treatments leveraging mAbs in the pipeline (see below for details on LLY's donanemab)

- **FDA has given BIIB a 2030 deadline to submit confirmatory trial data.** We think that the data will come in a lot sooner. BIIB will initiate further trials in May 2022, and aims to submit data by 2026. Recall both FDA and BIIB came under fire for the controversial approval for the exorbitantly priced treatment amid a series of questions BIIB's insufficient clinical trial design and Aduhelm's actual safety and efficacy. The drug was granted accelerated approval by FDA, as it was deemed to be a product addressing unmet need, where benefit outweighs risk. See here for full details of the BLA accelerated approval.

- **Health equity concerns: CMS lays out specific criteria mandating inclusion of underrepresented populations in subsequent trials.** According to the Alzheimer's Association, Alzheimer's and other dementias cost the US ~$355 B in 2021, disproportionately impacting Asian American, Black, Hispanic and Native American populations, Full report is here. Specially, CMS requires BIIB include patients with Alzheimer's and amyloid plaques in their study. Patients not meeting this criteria will not be covered. Furthermore, BIIB must submit statistically significant data proving improved cognition in trial participants and a detailed record of any adverse effects. If BIIB's post trial data does not show efficacy in these populations, he FDA has the authority to remove Aduhelm from the market.

Final NCD (for CMS.gov):

1) Monoclonal antibodies directed against amyloid that are approved by FDA for the treatment of AD based upon evidence of efficacy from a change in a surrogate endpoint (e.g., amyloid reduction) considered as reasonably likely to predict clinical benefit may be covered in a randomized controlled trial conducted under an investigational new drug application (IND).

2) Monoclonal antibodies directed against amyloid that are approved by FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry.

3) For CMS-approved studies, the protocol, including the analysis plan, must include:

a. A study population whose diversity of patients are representative of the national population with MCI due to AD or mild AD dementia.

b. A neurocognitive evaluation and instruments used to assess cognition and function for the clinical diagnosis of MCI due to AD or mild AD dementia for study enrollment and outcomes assessment.

c. A description of:

- The multidisciplinary dementia team and optimal medical management.

Contact Ipsita Smolinski - 202.250.3741 - Ipsita@capitol-street.com

- Study sites with clinical expertise and infrastructure to provide treatments consistent with the safety monitoring outlined in the FDA-approved label.

4) CMS-approved studies of antiamyloid mAbs approved by FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit must address all of the questions below:

a) Does the antiamyloid mAb meaningfully improve health outcomes (i.e., slowing in the decline of cognition and function) in broad community practice?

b) Do benefits and harms such as brain hemorrhage and edema, associated with use of the antiamyloid mAb, depend on characteristics of patients, treating clinicians, and settings?

c) How do the benefits and harms change over time?

Other thoughts:

- **CMS's decision mandates BIIB share data proving efficacy in under-represented populations.** According to the Alzheimer's Association, Alzheimer's and other dementias cost the US ~$355 B in 2021, disproportionately impacting Asian American, Black, Hispanic and Native American populations, Full report is here. If BIIB's post trial data does not show efficacy in these populations. the FDA has the authority to remove Aduhelm from the market.

- **Aduhelm's approval undermined confidence in FDA's integrity.** In November 2020, FDA statisticians called out BIIB and other FDA officials involved in Aduhelm's approval process for greenlighting the drug's approval based on inconclusive clinical trial results. Specifically, FDA statistician Tristan Massie cited the trials in questions for showing a "lack of substantial evidence, no replication, highly conflicting results in two studies, conflicting subgroup results." See presentation here, slide 3.

- **CMS designed the CED mechanism to expedite access to innovative technologies. BIIB must prove Aduhelm's efficacy in subsequent trials?** An ICER clinical review found that dosing did not impact the results in BIIB's trials, despite the company's claims. BIIB based its efficacy statement on extrapolating dosing from an earlier trial into a later trial. Susan Kremen (Cedars Sinai, and notably a PI for one of Aduhelm's trials) stated that the drug's approval was based on an amyloid pathology, a clinical biomarker that is NOT an indication of efficacy in preventing Alzheimer's.

- **Becerra advised CMS to reconsider increases to Medicare Part B premiums and deductibles since BIIB slashed Aduhelm's price in half.** Becerra issued a statement in Dec 2021 stating that BIIB's 50% price cut warranted a reconsideration of its increases to Part B premiums (+ $21.60 monthly) and deductibles ($30 annually) to cover possible costs to the Medicare system posed by Aduhelm. Note ~50% of the $21.60 monthly premium increase is allocated to the Supplementary Medical Insurance Trust Fund (SMI) for contingencies covering Aduhelm and other Alzheimer's treatments. 80% of patients eligible for Aduhelm will be Medicare beneficiaries. Recent reports show Aduhelm alone could double Part B annual drug spend.

Contact Ipsita Smolinski - 202.250.3741 - Ipsita@capitol-street.com