Evaluate Vantage

November 17, 2021

EU steers clear of Aduhelm as a bigger headache threatens

Amy Brown

Aduhelm's likely EU rejection comes amid a key senior executive departure and federal inquiry, and the drug now faces a crucial Medicare decision.

Biogen's Aduhelm has quickly become the most controversial drug of recent years, and today's news from the CHMP shows the EU regulator wanting no part of the drama. The agency's negative trend vote sets up the Alzheimer's drug to be rejected formally next month.

Many will shrug and ask, so what? It is true that EU was never going to be a big market for Aduhelm, but for Biogen the bad news keeps on coming. Monday saw the shock departure of Al Sandrock, the exec who had done more than most to champion Aduhelm, and next up is a US coverage decision that could invigorate – or completely stall – the drug's sales.

That the drug, approved in the US in June, has had a terrible launch is beyond doubt: sales from July to September amounted to just $300,000, and analysts do not expect things to get much better quickly. Biogen itself has blamed the sluggish launch on several issues.

But the company also claims that an ongoing review by Medicare, to decide who can receive the drug, is playing a big role. Before prescribing the Alzheimer's therapy, Biogen says, physicians are awaiting the outcome of a reimbursement decision known as a national coverage determination, to be made in the opening months of next year.

Given this uncertainty Monday's retirement of Mr Sandrock as Biogen's head of R&D came as a blow. It was largely thanks to Mr Sandrock that Biogen licensed in the drug that became Aduhlem, and thanks to him pivotal development, followed by an aggressive regulatory push, was pursued apparently against all odds.

Thus his retirement, against the backdrop of a federal inquiry into the FDA approval process and ongoing criticism of Aduhelm's pricing, is optically bad at the very least. And the drug's EU rejection will not help, even if, as Stifel points out, "it was hard to see the EMA going out on a limb and approving Aduhelm on its current dataset after all the [US controversy]".

But the upcoming reimbursement decision will be a hugely important event for Biogen, setting out which patients might be eligible for treatment.

What is a national coverage determination?

For those completely new to the US healthcare system let's back up one step. CMS (the Centers for Medicare & Medicaid Services) is the federal agency that, among its other responsibilities, administers the government-funded healthcare programme for the over 65s, called Medicare.

National coverage determinations, or NCDs, describe the conditions under which all Medicare contractors, nationwide, must provide and pay for an item or service. These are rarely undertaken; in the vast majority of cases usage is decided by local coverage determinations set by regional Medicare providers.

When it comes to drugs, Medicare will in most circumstances reimburse in line with an FDA approval. CMS sometimes has good reason to intervene, however, and in the case of Aduhelm several issues could have triggered the NCD process.

Questions about the drug's efficacy and the FDA's broad label have both caused controversy, as hasthe price that Biogen set. Given that Alzheimer's patients tend to be elderly, the US government will be footing the bill for the vast majority of prescriptions.

And there could be broader implications: "This NCD analysis will be applicable to national coverage considerations for aducanumab …. as well as any future monoclonal antibodies that target amyloid for the treatment of Alzheimer's disease," CMS said in a statement when it opened the NCD process in July.

What does an NCD entail?

The rigorous and wide-ranging process includes various stages of assessments, such as reviews of the clinical data by internal CMS staff, consultations with professional societies and consideration of their guidelines, and external technology assessments. There are also periods during which public comments are solicited and considered.

Make no mistake, this is a serious business. The process is established by statute and is designed to determine whether the evidence backing Aduhelm meets legal requirements for reimbursement by Medicare. The law states that items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury".

By law, CMS cannot consider the cost of treatment under the NCD process. However, it is hard to believe that Aduhelm's $56,000 per year price will not feature in these considerations in some way.

How long will it take?

Potentially up to nine months. A proposed NCD, expected by January 12, will then be opened up to a 30-day public comment period. A final decision is likely three months later, in early April.

What remains unknown is whether CMS will convene a Medicare Evidence Development & Coverage Advisory Committee (Medcac). This provides independent guidance and expert advice, and was widely expected to be set up for Aduhelm.

A Medcac has not been announced so far, however. The intense scrutiny around Aduhelm's approval and how politicised the whole situation has become has perhaps made assembling such a committee difficult.

What are the potential outcomes?

There are five main possibilities, as described by Biogen and analysts.

Firstly non-coverage, though few see this as likely. In the last 15 years no FDA-approved drug has been fully denied, according to analysts. If Medicare does say no, the burden could shift to Medicaid, which is bound by law to cover all FDA-approved drugs.

Alternatively, CMS could grant full coverage to the label. Again, this outcome is considered unlikely, but would represent a huge win for Biogen.

A third option is for CMS to leave the coverage decision up to Medicare Administrative Contractors, local, private healthcare insurers responsible for administering Medicare claims. Given the high-profile nature of this situation, which is crying out for a national decision, this would be a big surprise.

Coverage with evidence development (CED) is a possibility. This instrument, which has historically been used with devices rather than drugs, would see Aduhelm conditionally covered while further data are gathered in a clinical study.

Stifel analysts wrote that a CED would likely prove expensive and complicated for CMS to implement. Investors would also consider this a bad outcome for Biogen, as CMS would only pay for Aduhelm's use in the study.

The fifth possible outcome is that CMS will cover Aduhelm, but with restrictions beyond the label; the prevailing view is that this is the most likely scenario. Biogen itself has pointed out that, of the 12 NCDs of drugs carried out by CMS, 10 were ultimately covered with restrictions.

This would see the eligible patient population narrowed from Aduhelm's current indication, which merely describes those with mild Alzheimer's disease. The extent of CMS's restrictions is the big unknown here, though there are obvious options, such as confirmation of the presence of amyloid plaques on a PET scan, or use of some of the inclusion/exclusion criteria that Biogen specified in the Engage and Emerge clinical trials, Stifel suggests.

Other battles

Given Aduhelm's woeful third-quarter sales, coverage with restrictions would probably be considered a win right now. In reality, however, lack of CMS guidance is not the only battle the company is fighting.

Scepticism from physicians and patients will also be hampering uptake; to this end Biogen has promised more clinical data, to confirm Aduhelm's benefits, in the coming months. But an EU rejection, even if not entirely unexpected, will do nothing to improve the drug's perception.

And, of course, the competition is not standing still. Important events are looming for competing amyloid-beta antibodies, whose progress or otherwise will also have a bearing on Aduhelm's stuttering launch.

Swing events: approaching readouts and decisions for the amyloid-beta antibodies

Date	Project	Event	Debate
By end of 2021	Donanemab	**Lilly** aims to file for US accelerated approval	Will the FDA approve under AA before ph3 Trailblazer-Alz 2 data?
By end of 2021	Lecanemab (BAN2401)	**Eisai/Biogen** aims to complete rolling submission for AA	Will FDA approve under AA before ph3 Clarity-AD data?
H2 2022	Gantenerumab	**Roche** to report data from ph3 Graduate programme	Will Roche file for AA before these data?
H2 2022	Donanemab	**Lilly** to launch donanemab, assuming AA is granted	–
Q3 2022	Lecanemab (BAN2401)	**Eisai/Biogen** to report phase 3 Clarity-AD data	–
H1 2023	Donanemab	**Lilly** to report ph3 Trailblazer-Alz 2 data	If this and other ph3 trials disappoint, will FDA revoke Aduhelm's approval?

Source: company statements.

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Evaluate HQ
44-(0)20-7377-0800

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754

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