Better 8 years late than never: Merck KGaA nabs FDA nod for MS drug Mavenclad

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Merck KGaA has won FDA approval for oral multiple sclerosis treatment Mavenclad, eight years after its rejection. (Merck KGaA)

Up to 10 years of safety data has paid off for Merck KGaA's oral multiple sclerosis treatment Mavenclad. The drug has returned from the dead, eight years after an FDA rejection dashed its dream of challenging Novartis' then-newly-minted Gilenya—and according to one analyst, it might just be a blockbuster.

Mavenclad (cladribine) is now **approved** to treat relapsing forms of MS, including relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS), the FDA said Friday. The agency's green light came after more than 50 other countries, including in the EU, had approved it.

The Merck drug does carry a black box warning for an increased risk of cancer and birth defects, which pushed its FDA-approved use into the second line—in patients who don't respond to or are unable to tolerate other MS drugs. But as Bernstein analyst Wimal Kapadia sees it, the safety profile is no reason to belittle Mavenclad's success potential.

The FDA originally slapped Mavenclad with a complete response letter back in 2011, citing the need for more safety and efficacy data. The company initially canned the development program, but didn't give up entirely. It followed its trial patients for years afterward, and the combined data ended up forming the basis for its new submission to the FDA.

In clinical data from 1,976 patients—24% of whom were tracked for eight years—Mavenclad **reduced** the annual relapse rate by 58% compared to placebo when given as an oral treatment for a maximum of 20 days during a two-year period. 81% of Mavenclad patients were relapse-free, versus 63% in the control group, according to Merck. That kind of efficacy puts Mavenclad at the upper end among its peers, alongside Biogen's Tecfidera and Gilenya.

Dosing is where Mavenclad stands out; it's given in two courses of five tablets one month apart in the first and second year. There are of course the obviously less convenient injection drugs, and most oral products require daily

Given the efficacy profile, superior dosing schedule and its safety outside of the cancer warning—it bears no infection risks common to MS drugs—Kapadia argues that "Mavenclad is well positioned." In a Monday note to clients, the Bernstein analyst pegged the drug at €650 million ($730 million) in 2025 U.S. sales, and another €465 million in EU, where the drug has been approved since August 2017. Combined, that puts Mavenclad in blockbuster territory.

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Mavenclad's label isn't ideal. On the positive side, the label specifically approves the drug for SPMS, and the only other real competitor that boasts the same indication is Novartis' Mayzent, approved just last week. In Kapadia's view, that nod confirms Mavenclad's use in more severe cases of MS.

As for the malignancy warning? Kapadia said the problem isn't just seen in Mavenclad. Many approved disease-modifying drugs in RRMS, including Gilenya, Ocrevus, Biogen's Tysabri and Sanofi's Lemtrada, also tend to present that risk, and therefore the warning shouldn't be considered "a major hindrance" to Mavenclad.

The FDA originally flagged concerns of higher cancer risks associated with Mavenclad, but Merck defeated the claim, thanks in part to a 2015 **study** that ran a meta-analysis of 11 phase 3 trials from seven disease-modifying MS drugs. The study found that the control arm in Mavenclad's phase 3 trial, dubbed Clarity, had the lowest rate of malignancies. That placebo arm's cancer rate came in significantly less than the combined control rate for all other trials, meaning that Clarity's results may have been unfairly skewed by an abnormally low cancer rate in control patients.

Now, on the negative side: "Being a second-line option is no bad thing, but having it clearly spelled out on the label is not helpful," Kapadia said.

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The analyst noted that Mavenclad is the only other MS drug recommended in later lines, with "notoriously unsafe" Lemtrada reserved for third-line treatment, "something that we feel unfairly draws attention to what is actually not that bad a safety profile." Still, according to Merck Chairman and CEO Stefan Oschmann on the company's fourth-quarter conference call, 30% of Mavenclad use in Germany is in treatment-naïve patients.

But in a risk unique to Mavenclad, the black box warning forbids Mavenclad from use in pregnant women and in women and men who intend to have a baby during treatment or within six months after therapy. As MS is more common in women, Kapadia suspects the warning could hurt sales. But given that Ocrevus, Tecfidera, Tysabri and Lemtrada all do not recommend use in pregnancy based on animal data, Kapadia wondered to what extent the warning could affect actual uptake.

More MS competition could be coming Merck's way, though. One year after its own FDA setback, Celgene recently refiled for FDA approval of ozanimod in relapsing MS. Like Mayzent, the drug is an oral S1P receptor modulator.

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