BIOPHARMADIVE

FDA documents hint at ‘uphill battle’ for broad approval of Sage’s depression drug

New information from the agency’s review show it had concerns about the side effects experienced by people with major depressive disorder who took Sage’s drug, Zurzuvae.

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The Food and Drug Administration’s decision last month not to approve a new treatment for one of the most common forms of depression was, in part, due to safety concerns, according to newly released documents detailing the agency’s review process.

The treatment, now known as Zurzuvae, was developed by Massachusetts-based biotechnology company Sage Therapeutics. Through a series of late-stage clinical trials, Sage tested Zurzuvae as a potential therapy for both postpartum depression and major depressive disorder. Results from the postpartum study were generally positive, showing the medicine quickly and significantly improved depressive symptoms.

The data in major depressive disorder were more mixed, however. A key study failed in 2019, leading Sage to redraw its development plans. And while more recent trials were successful, Zurzuvae’s effects in these patients appeared to be modest overall and wane with time.

Still, Sage and its partner Biogen believed they had gathered enough supportive data to submit Zurzuvae for approval in both conditions. The FDA agreed to review the companies' approval application in February, and, by early August, had decided to clear the drug for use in postpartum depression but reject it for major depressive disorder.

Though large sections are redacted, documents from the FDA's review give a better sense of why the agency issued a split decision.

In evaluating Zurzuvae's potential benefits and risks, the FDA noted how so-called serious adverse events were reported throughout the development program. Some patients were in confused states days after beginning treatment, while others experienced unusual physical weakness or lack of energy.

In an early-stage study that used a different dose and formulation of Zurzuvae than what's now approved, a 26-year-old male patient was "unresponsive to stimuli" for 50 minutes and had trouble feeling pain. Another participant, a 28-year-old male, had a nearly five-hour-long episode after taking Sage's drug, during which he was unresponsive to pain stimuli, documents said.

The FDA also homed in on a small number of major depressive patients who reported having suicidal thoughts and behavior after either receiving Zurzuvae or going off the drug.

"There was no signal for suicidal ideation and behavior in the [postpartum] studies," FDA staff wrote. "However, because there was a signal in the [major depressive disorder] studies, and we cannot rule out an effect, we will include suicidal thought and behavior warning language" in the drug's potential label.

Previously, Sage indicated that studies of its drug had not shown signs of suicidal thoughts or behaviors. The FDA's view on Zurzuvae's safety profile therefore "does not appear completely

aligned with Sage's historical interpretations," according to Brian Abrahams, an analyst at the investment firm RBC Capital Markets.

The FDA "may not perceive the benefits … as ever outweighing potential [safety] risks of the drug … even with additional data," Abrahams wrote in a note to clients Thursday. He added that Sage is likely to face a "uphill battle" if the company has any plans to try again at getting Zurzuvae approved in major depressive disorder.

For Sage, the rejection has proven to be a substantial setback.

Major depressive disorder — which affects tens of millions of people in the U.S. by some estimates — was central to the Wall Street models that had pegged Zurzuvae as a blockbuster product. Without an approval there, the commercial opportunity for the drug is much smaller. Abrahams and his team, for instance, estimate around $240 million in annual peak sales for Zurzuvae in postpartum depression.

Against these lower sales estimates, Sage this week announced that it will lay off roughly 40% of its workforce as part of a larger restructuring meant to save money and prioritize certain research programs.

Sage also said two executives who've been with the company since its founding, Chief Scientific Officer Al Robichaud and Chief Development Officer Jim Doherty, will be leaving, though Robichaud will continue on as a scientific consultant and adviser. Mark Pollack, senior vice president of medical affairs, will depart as well.

Sage shares currently trade at about $20 apiece, roughly half of their value at the start of the year.